**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Van Beusechem

Examiner: Scott Long

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For: VIRUSES WITH ENHANCED LYTIC POTENCY

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Lauren T. Emr
(Printed Name)

Signature: /Lauren T. Emr/

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

**DECLARATION OF FRANK MCCORMICK, PHD, FRS UNDER 37 C.F.R. § 1.132**

I, Frank McCormick, PhD, FRS, declare as follows:

1) I am Director of the Helen Diller Family Comprehensive Cancer Center & Cancer Research Institute of the University of California, San Francisco (UCSF). I was founder and Scientific Director of Onyx Pharmaceuticals and as such have been actively involved in pre-clinical and clinical development of oncolytic adenoviruses, amongst which the ONYX-OIS product which has been tested in various clinical studies. I have been practicing in the field of adenovirus gene therapy for 18 years. A copy of my *curriculum vitae* is attached hereto as Exhibit A.

2) I have read U.S. Patent Application No. 10/501,407 and the related office actions dated July 6, 2010 and December 2, 2010. In particular, I have read the comments from the examiner that claims 26-35 and 38-40 are obvious in view of Curiel et al. (US-6,824,771) and

Xu et al. (Human Gene Therapy 1997; 8:177-185), and that claims 36-37 are obvious over the same references also in view of Lin et al. (Cancer Research 2000; 60:5895-5901). I have also read the response by the applicant thereto filed on November 8, 2010, and the references Curiel et al., Xu et al., and Lin et al. I understand that similar objections have been raised by the examiner based on the combination of Hallenbeck et al (Human Gene Therapy 1999; 10:1721-1733) and Lin et al.; and Fueyo et al. (Oncogene 2000; 19:2-12) and Lin et al. Therefore, I have also read Hallenbeck et al and Fueyo et al.

3) The unexpected discovery that the addition of a gene expressing p53 to a conditionally replicating adenovirus increased efficacy was, in my opinion, highly novel and certainly not predictable from available research publications, at the time the instant application was filed. Specifically, it was not predictable from the teachings of Curiel et al., Xu et al., or Lin et al., or from a combination thereof. The Hallenbeck et al. and the Fueyo et al. references resemble the Curiel et al reference in that they address oncolytic viruses, albeit that the specific oncolytic virus is different from the one discussed by Curiel et al.

4) The fact that the oncolytic virus was slightly different is not of particular relevance. As stated above, the finding that the addition of a gene expressing p53 to a conditionally replicating adenovirus increased efficacy was, in my opinion, highly novel and certainly not predictable from previous research publications.

5) On the contrary, at the time the instant application was filed, it was expected that restoration of functional p53 would suppress viral replication, as suggested by Hermiston and Kuhn (Cancer Gene Therapy, 2002; 9:1022-1035) and others. This is because p53 is actively degraded during viral replication, and adenoviruses that fail to degrade p53 are defective for replication in normal primary human cells (O'Shea et al., Cancer Cell, 2004; 6:611-623). This view was re-enforced recently by O'Shea and coworkers (Soria et al., Nature 2010; 466: 1076-1081) who showed that adenoviral E4 proteins contribute to inactivation of p53 during infection, in addition to the well-known effect of EIB 55K on p53 degradation. Therefore, restoration of

functional p53 would be expected to suppress virus replication rather than enhancing it. A copy of Soria et al. is attached as Exhibit B.

6) Another surprising aspect of the instant application's discovery is that p53 expressed in an adenovirus remains functional at all. Adenoviruses shut down host protein synthesis and synthesis of viral genes expressed from certain early promoters. It was therefore unexpected that p53 could remain functional (documented in van Beusechem et al., Cancer Research 2002; 62:6165-6171) and promote expression of downstream genes. The recent work of Soria et al. cited above also underscores the fact that adenoviruses encode multiple mechanisms to eradicate and inactivate p53 during infection: the activity demonstrated by the instant invention was therefore unexpected for several distinct reasons.

7) The idea that direct, forced, expression of p53 in a p53-negative tumor cell promotes growth arrest, or cell death, has been well established for many years. However, this effect is clearly distinct from the novel role of p53 in promoting virus replication, as discovered in the instant application. The importance of the instant invention is based on the presumption that clinical efficacy depends on robust virus replication and infection of multiple tumor cells, rather than direct killing of a single transduced cell by a non-replicating viral vector.

8) For these reasons, I believe that the concepts underlying the instant patent application are novel and were not at all predictable/obvious based on prior publications or disclosures, at the time of the invention.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed:_____ Dated:_____

Dr. Frank McCormick

ARTICLES

# Heterochromatin silencing of p53 target genes by a small viral protein

Conrado Soria[1]*, Fanny E. Estermann[1]*, Kristen C. Espantman[1] & Clodagh C. O'Shea[1]

The transcription factor p53 (also known as TP53) guards against tumour and virus replication and is inactivated in almost all cancers. p53-activated transcription of target genes is thought to be synonymous with the stabilization of p53 in response to oncogenes and DNA damage. During adenovirus replication, the degradation of p53 by E1B-55k is considered essential for p53 inactivation, and is the basis for p53-selective viral cancer therapies. Here we reveal a dominant epigenetic mechanism that silences p53-activated transcription, irrespective of p53 phosphorylation and stabilization. We show that another adenoviral protein, E4-ORF3, inactivates p53 independently of E1B-55k by forming a nuclear structure that induces *de novo* H3K9me3 heterochromatin formation at p53 target promoters, preventing p53–DNA binding. This suppressive nuclear web is highly selective in silencing p53 promoters and operates in the backdrop of global transcriptional changes that drive oncogenic replication. These findings are important for understanding how high levels of wild-type p53 might also be inactivated in cancer as well as the mechanisms that induce aberrant epigenetic silencing of tumour-suppressor loci. Our study changes the longstanding definition of how p53 is inactivated in adenovirus infection and provides key insights that could enable the development of true p53-selective oncolytic viral therapies.

Tumour mutations and DNA virus proteins converge in inactivating p53 (ref. 1), which was initially discovered as a cellular target of SV40 Large T[2,3]. However, despite 30 years of research, the critical factors that determine p53-activated transcription are still not fully understood[4,5]. p53 is expressed constitutively in normal cells where its activity is limited by p53 protein degradation[6]. p53 activation is triggered in response to oncogenes and DNA damage, which stabilize p53 (refs 7–9). This has led to the general belief that the induction of p53 levels and phosphorylation[10] is synonymous with p53-activated transcription. As such, the induction of p53 levels is a standard readout for p53 activation and rationale for several cancer therapies, including irradiation and genotoxic drugs[11], MDM2 antagonists[12], and the E1B-55k-deleted oncolytic adenoviral therapy, ONYX-015 (ref. 13).

The adenoviral protein, E1B-55k, binds to the p53 transactivation domain and is sufficient to inactivate p53 in cellular transformation[7,14]. In infection, E1B-55k forms a complex with another adenoviral protein, E4-ORF6, which recruits a cellular ubiquitin ligase that targets p53 for degradation[15,16]. The degradation of p53 by E1B-55k is thought to be the critical event that inactivates p53 for virus replication[17]. An E1B-55k-deleted virus[18], *dl*1520/ONYX-015, induces high p53 levels, which was expected to limit viral replication in normal cells but not p53 mutant tumour cells[13]. On this basis, ONYX-015 (ref. 13) was tested in patients as a p53 tumour-selective oncolytic viral therapy[19,20] and is now approved in several countries (known as Oncorine). However, the loss of E1B-55k functions in viral RNA export, rather than p53 inactivation, is the major determinant of ΔE1B-55k tumour selectivity[21,22]. Contrary to expectations, although p53 accumulates to high levels in the nucleus of ΔE1B-55k (Δ55k)-infected human primary small airway epithelial cells (SAECs), the physiological target cells for adenovirus infection, p53 transcriptional targets, such as *p21* (also known as *CDKN1*), *MDM2*, *CCNG*, *14-3-3σ* (also known as *SFN*), *PERP*, *PIG3* (also known as *TP53I3*) and *GADD45*, are not induced (Fig. 1a and ref. 21). The failure of p53 stabilization to activate transcriptional targets is not a tissue-specific effect and occurs in multiple primary cell types and tumour cell lines (Supplementary Figs 1–3), including U2OS tumour cells where p53 targets are suppressed to a similar extent as that in cell-lines with p53 mutations. This reveals a fundamental gap in our understanding of not only adenovirus biology but also p53 activation.

## p53 stabilization without activity

Cellular and viral oncogenes, such as *Ras* and adenovirus *E1A*, trigger p53 activation by inducing the expression of ARF[9], which inhibits MDM2-mediated p53 degradation. ARF is lost in 58% of cancers[9], which had previously been invoked as the critical factor that prevents p53 activation in ΔE1B-55k-infected tumour cells[23]. Using a U2OS stable cell-line (p53 wild-type, ARF negative) in which ARF expression is induced by isopropyl-β-D-thiogalactopyranoside (IPTG), we show that ARF stabilizes p53 and activates p21 transcription in mock infection. Nevertheless, although ARF expression increases basal p53 activity, the induction of p21 is repressed in both wild-type- and ΔE1B-55k-infected cells (Fig. 1b and Supplementary Fig. 4). Furthermore, endogenous ARF induction also fails to activate p53 targets in ΔE1B-55k-infected SAECs (Fig. 1a). Thus, p53 is inactivated, irrespective of E1B-55k and ARF expression in adenovirus-infected cells.

DNA damage signals also have a critical role in activating p53, triggering p53 phosphorylation and protein stabilization[8,24]. In clinical trials, ΔE1B-55k (ONYX-015), was used in combination with genotoxic chemotherapies, such as 5-fluorouracil[19,20]. We reasoned that the induction of p53 levels alone may not be sufficient to activate p53 in infected cells, and that DNA damage is also required. However, 5-fluorouracil fails to activate p53 in ΔE1B-55k-infected U2OS cells (Supplementary Fig. 5). The DNA damage checkpoint is deregulated in many tumour cells. Therefore, we also analysed ΔE1B-55k-infected SAECs and show that p53 transcriptional targets cannot be activated by γ irradiation (Fig. 1c and Supplementary Fig. 6),

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*These authors contributed equally to this work.

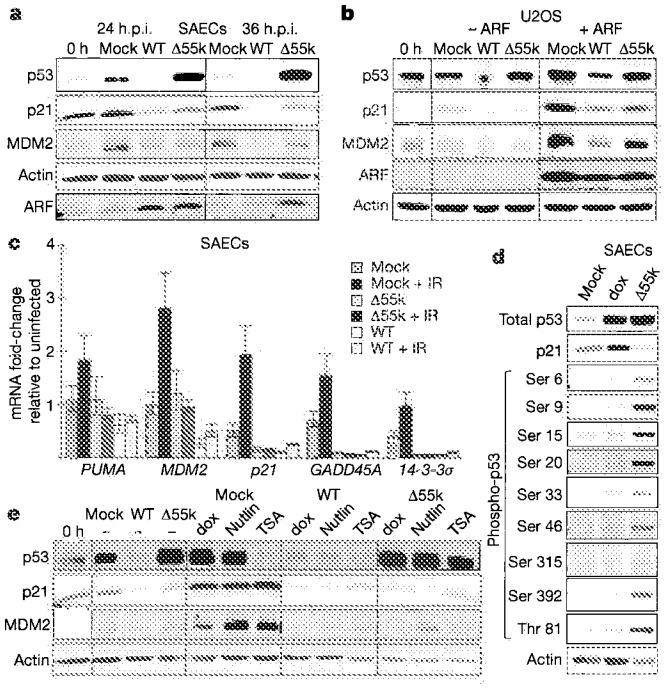


**Figure 1 | p53 is induced and phosphorylated in ΔE1B-55k infection but p53 activity is dominantly suppressed.** **a**, SAECs were infected and protein lysates analysed by immunoblotting. **b**, U2OS cells with inducible *ARF* were infected as indicated and analysed for p53 levels and activation by immunoblotting. **c**, RT–qPCR of p53 transcriptional targets in infected SAECs (36 h.p.i.) ±10 Gy γ irradiation (IR). Error bars represent s.d. ($n = 3$). **d**, Immunoblot of p53 protein phosphorylation in infected or doxorubicin (dox)-treated SAECs (36 h.p.i.). **e**, Immunoblot of SAECs (36 h.p.i.) infected as indicated and treated with either control (−), dox, nutlin, or TSA at 24 h.p.i.

ultraviolet irradiation (Supplementary Fig. 7) or doxorubicin (dox, Fig. 1e).

The activation of p53 in response to DNA damage is mediated via kinases, such as ATM, ATR, DNA-PKcs (also known as PRKDC), CHK1 and CHK2, which phosphorylate p53 (ref. 8) at key residues, stabilizing p53 and potentiating p53–DNA binding[24]. A possible explanation for the failure of DNA damage to activate high p53 levels in ΔE1B-55k-infected cells is that p53 phosphorylation is inhibited by viral infection. However, even without the introduction of exogenous genotoxic stress, p53 is already highly phosphorylated at multiple sites targeted by DNA damage kinases in ΔE1B-55k-infected SAECs (Fig. 1d). Thus, although oncogenes and DNA damage trigger p53 stabilization and phosphorylation in ΔE1B-55k-infected cells, p53 fails to activate the transcription of downstream effectors.

We next examined if, in the absence of E1B-55k, MDM2 binds and inactivates p53 in adenovirus-infected cells. Nutlin is a small molecule antagonist that inhibits MDM2-p53 binding[12]. In contrast to mock, nutlin fails to stabilize p53 further or induce p21 in ΔE1B-55k-infected SAECs (Fig. 1e). The histone deacetylase (HDAC) inhibitor, trichostatin A (TSA), induces the expression of p21 independently of p53 stabilization or phosphorylation (Fig. 1e). However, in ΔE1B-55k-infected cells, TSA fails to induce p21. We conclude that p53 transcriptional targets are dominantly suppressed in adenovirus-infected cells, irrespective of E1B-55k, and cannot be activated in response to radiation, genotoxic drugs, ARF, MDM2 antagonists or HDAC inhibitors.

## E4-ORF3 inactivates p53 independently of E1B-55k

Our data strongly indicate that there is a previously undiscovered adenoviral protein that inactivates p53 independently of p53 degradation. To test this, we screened for p53 activation in primary cells infected with adenoviruses that have compound mutations in E1B-55k and other early viral genes (Supplementary Fig. 8). In addition to deleting E1B-55k, the loss of either E1A-13s or E4-ORF3 is required to activate p53 in infected cells (Fig. 2a). This is surprising, especially because *E1A* is a potent oncogene that triggers p53 activation in cellular transformation[7,14]. In adenovirus infection, the E1A-13s splice form is required for the transactivation of other viral genes[17], including E4-ORF3 (Fig. 2a). Consistent with this, we show that, in contrast to GFP (green fluorescent protein), the ectopic expression of E4-ORF3 rescues p53 inactivation in both ΔE1B-55k/ΔE4-ORF3- and ΔE1B-55k/ΔE1A-13s-infected cells (Fig. 2b). The slight reduction of p21 by Ad-GFP in ΔE1B-55k/ΔE4-ORF3 co-infection is due to the partial activation of E4-ORF3 transcription (in *trans*) by E1A-13s, which does not occur in ΔE1B-55k/ΔE1A-13s co-infection (Supplementary Fig. 9). Hence, E1A-13s induces the expression of E4-ORF3, which then inactivates p53 via an E1B-55k-independent mechanism. Moreover, the expression of E4-ORF3 alone is also sufficient to inhibit p53 activation (Supplementary Fig. 10). These data reveal E4-ORF3 as a novel adenoviral protein that inactivates the p53 tumour-suppressor pathway.

The proposed p53 tumour selectivity of the ΔE1B-55k oncolytic therapy, ONYX-015, is based on p53 stabilization being the sole critical event that determines p53-activated transcription. Although there is

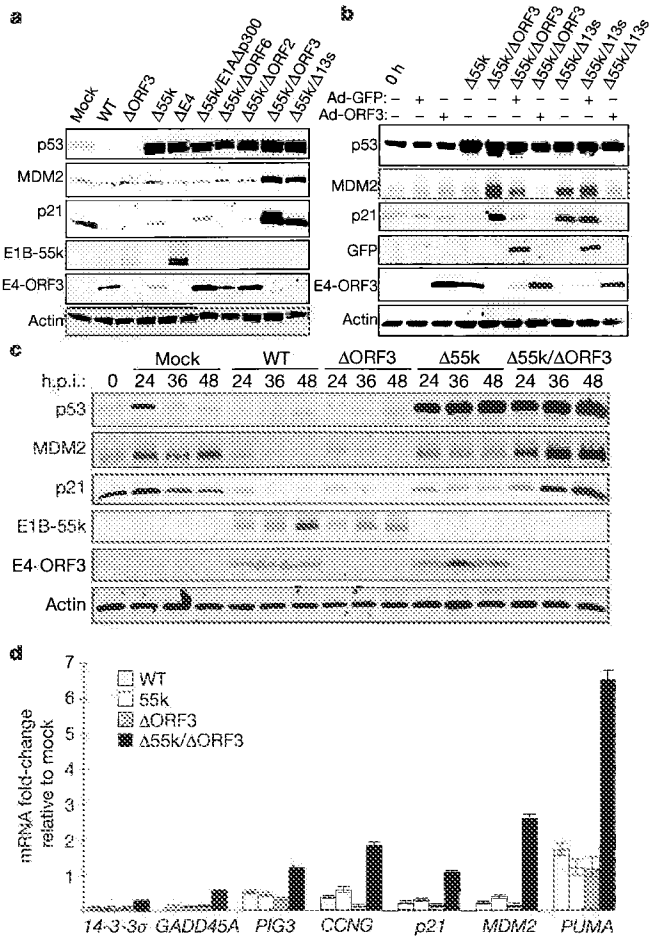


**Figure 2 | E4-ORF3 inactivates p53 independently of E1B-55k and p53 degradation.** **a**, SAECs were infected with the indicated viruses (detailed description in Supplementary Fig. 8) and protein lysates (36 h.p.i.) were analysed for p53 activation by immunoblotting. **b**, SAECs were co-infected as indicated with either a GFP control virus (Ad-GFP, +) or a virus expressing E4-ORF3 (Ad-ORF3, +). Protein lysates (36 h.p.i.) were analysed for p53 activation by immunoblotting. **c**, SAECs were infected and harvested over a 48 h time course as indicated and analysed for p53 activation by immunoblotting. **d**, RT–qPCR of p53 transcriptional targets in infected SAECs at 36 h.p.i. Error bars represent s.d. ($n = 3$).

some basal p53 activity in ΔE1B-55k-infected cells compared to wild-type virus, the additional deletion of E4-ORF3 is necessary for p53 to activate downstream effectors over the course of infection (Fig. 2c, d). In contrast to p53 transcriptional targets, the mRNA levels of p53 and the housekeeping gene, *GUSB*, are not impacted by E4-ORF3 (Supplementary Fig. 11). p53 stabilization is required to activate p53 transcriptional targets, and does not occur in ΔE4-ORF3 infection where p53 is degraded by E1B-55k/E4-ORF6. Furthermore, using a p53-inducible stable cell-line (H1299-D1, Supplementary Fig. 12), we show that the induction of p21 and MDM2 in ΔE1B-55k/ΔE4-ORF3 infection is p53-dependent. Thus, the deletion of both E1B-55k and E4-ORF3 is necessary to activate p53 in adenovirus infection. We conclude that E4-ORF3 has a critical and novel role in inactivating p53 independently of E1B-55k and p53 degradation.

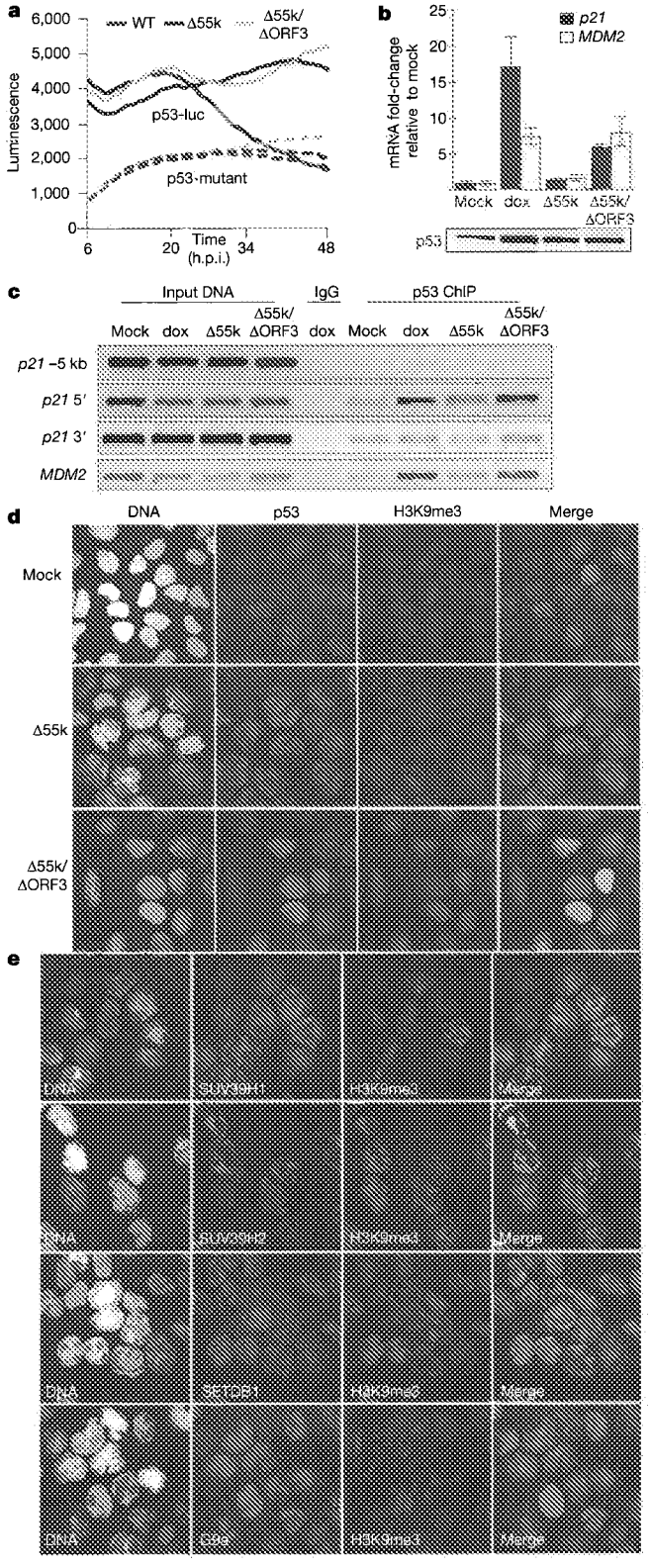


**Figure 3 | E4-ORF3 induces heterochromatin formation and prevents p53–DNA binding at endogenous promoters. a**, U2OS cells were transfected with p53-luc (solid line) or p53-mutant (dashed line) luciferase plasmids and infected with indicated viruses. Luminescence is plotted against time. **b**, **c**, U2OS cells were infected as indicated or treated with doxorubicin. **b**, p53 induction was analysed by immunoblotting and p53 transcriptional targets quantified by RT–qPCR (36 h.p.i.). Error bars represent s.d. ($n = 3$) **c**, p53 ChIPs were analysed by semiquantitative PCR for *p21* and *MDM2* promoter sequences. **d**, p53 (green) and H3K9me3 (red) immunofluorescence of infected U2OS cells (36 h.p.i.). **e**, Localization of SUV39H1, SUV39H2, SETDB1 and G9a (green) with H3K9me3 (red) in Δ55k-infected U2OS cells (36 h.p.i.).

### E4-ORF3 prevents p53–DNA binding at chromatin

DNA tumour virus proteins, such as E1B-55k, SV40 LT and HPV E6, inactivate p53 via direct high affinity protein–protein interactions[1]. However, contrary to this established paradigm, E4-ORF3 does not co-localize with p53 (Supplementary Fig. 13) or co-immunoprecipitate with p53 (data not shown). This indicates that E4-ORF3 inactivates p53 via a non-canonical mechanism.

The induction of p53 levels and phosphorylation induces p53 conformational changes that drive sequence-specific DNA binding and the recruitment of transcription co-factors[25]. A p53–DNA binding domain that is competent to bind to DNA can be distinguished by immunoprecipitation with monoclonal antibody PAb1620 versus PAb240 (ref. 26). p53 is immunoprecipitated selectively by PAb1620 in both ΔE1B-55k- and ΔE1B-55k/ΔE4-ORF3-infected cells (Supplementary Fig. 14), demonstrating that the p53 DNA-binding domain is in a protein conformation that should be capable of binding to DNA[26] in both cases. To determine functionally if E4-ORF3 prevents p53–DNA binding, we transfected U2OS cells with a p53 luciferase plasmid (p53-luc), where p53 binding to consensus DNA sequences activates luciferase transcription[27]. A control pGL3-luciferase reporter (non-p53 promoter) is activated to similar levels in all viral infections (Supplementary Fig. 15). In wild-type-virus-infected cells, p53-activated transcription of luciferase is inhibited after 24 h (Fig. 3a), which is expected due to p53 degradation. In contrast, p53-luciferase is activated in both ΔE1B-55k and ΔE1B-55k/ΔE4-ORF3 infection (Fig. 3a). The induction of luciferase requires p53–DNA binding, since a mutated p53 response element (p53-mutant) abolishes luciferase activity. These experiments demonstrate that E4-ORF3 does not compete with p53 for binding to consensus DNA target sequences or prevent p53 transcriptional activation of promoters in ectopic reporter plasmids.

The ability of E4-ORF3 to prevent p53-activated transcription of endogenous targets, but not ectopic p53-luciferase plasmids, is at first difficult to reconcile. Plasmid DNA is not subject to the same architectural and packing constraints as DNA in cellular chromatin. Therefore, we performed p53 chromatin immunoprecipitations (ChIPs) to determine if E4-ORF3 specifically prevents p53–DNA binding in the context of cellular chromatin. p53 binding to target sites in the *p21* (5′ and 3′ site) and *MDM2* promoters[25] is induced upon doxorubicin treatment and ΔE1B-55k/ΔE4-ORF3 infection, where it activates the transcription of *p21* and *MDM2* RNAs (Fig. 3b, c). In contrast, although p53 is induced to similar levels, E4-ORF3 prevents p53–DNA binding to the *p21* and *MDM2* promoters in ΔE1B-55k-infected cells (Fig. 3b, c and Supplementary Fig. 16). Thus, E4-ORF3 inactivates p53 by preventing p53 binding to DNA target sites specifically in the context of cellular chromatin.

### Repressive histone methylation silences p53 targets

We reasoned that p53–DNA binding depends not only on the protein conformation of p53 but also the accessibility of target promoters in the cellular genome. We proposed that E4-ORF3 could inactivate p53 by inducing heterochromatin at endogenous target promoters, preventing the access of p53 to DNA. Heterochromatin compaction is specified by the loss of histone acetylation and induction of repressive histone methylation[28]. TSA fails to induce p21 in ΔE1B-55k-infected SAECs (Fig. 1e), indicating that E4-ORF3 inactivates p53 targets via a mechanism that is dominant to the inhibition of histone deacetylation. In cancer, the aberrant epigenetic silencing of tumour-suppressor genes, such as *p16*$^{INK4a}$ (also known as *CDKN2A*), is initiated by the methylation of histone H3 at lysine 9 (H3K9)[29]. p53 localization is indistinguishable in ΔE1B-55k- and ΔE1B-55k/ΔE4-ORF3-infected cells (Fig. 3d). However, in ΔE1B-55k-infected cells, where p53 is inactive, dense regions of H3K9me3 repressive heterochromatin are induced at the periphery of the nucleus (Fig. 3d and Supplementary Fig. 17). Of the four known methyltransferases that catalyse H3K9 trimethylation (H3K9me3), we show that SUV39H1 and SUV39H2 (which share 59% sequence identity and have redundant functions)[30,31], but not SETDB1 (ref. 32) or G9a (also known as EHMT2, ref. 33), are specifically associated with the formation of *de novo* H3K9me3 heterochromatin domains in ΔE1B-55k-infected nuclei (Fig. 3e). The formation of these domains requires E4-ORF3 and does not occur in either mock- or ΔE1B-55k/ΔE4-ORF3-infected cells (Supplementary Figs 18–21).

These data demonstrate that E4-ORF3 induces novel H3K9me3 heterochromatin, which could deny p53 access to endogenous target promoters. To test this, we performed p53 and H3K9me3 ChIPs. The induction of repressive heterochromatin by E4-ORF3 is not associated with a global upregulation of either total histone H3 or H3K9me3, which are at similar levels in all infections (Fig. 4a). In ΔE1B-55k/ΔE4-ORF3-infected cells, p53 binding is induced at *p21* and *MDM2* promoter sites (consistent with Fig. 3c), whereas H3K9me3 is at a similar level to an IgG-negative control (Fig. 4a and Supplementary Fig. 22). In contrast, in ΔE1B-55k-infected cells, H3K9me3 is enriched at the *p21* and *MDM2* promoters where p53 binding is prevented. H3K9me3 is also induced at the −5 kb region of the *p21* promoter and is not restricted to p53 binding sites (Supplementary Fig. 22). Thus, in cells expressing E4-ORF3, there is an inverse correlation between p53 and H3K9me3 at p53-regulated promoters. The same conclusions were reached for additional p53 targets, including *GADD45A*, *FAS*, *PUMA* (also known as *BBC3*) and *PIG3* (Supplementary Figs 22–24). In contrast, at non-p53-regulated promoters, such as *ACTIN* (also known as *ACTA*) and *POLR2*, H3K9me3 is not induced in ΔE1B-55k-infected cells relative to mock (Supplementary Figs 22 and 24). Basal H3K9me3 is decreased at these promoters in ΔE1B-55k/ΔE4-ORF3-infected cells, indicating that E4-ORF3 may also restrain global demethylase activity. We conclude that E4-ORF3 inactivates p53 by inducing *de novo* H3K9me3 heterochromatin silencing at p53 target promoters. With access denied, p53 is powerless to activate the transcription of downstream effectors.

The induction of heterochromatin formation is still relatively poorly understood. Thus, a major question is how is E4-ORF3 directly involved in inducing repressive H3K9me3 heterochromatin at p53 target promoters? E4-ORF3 does not co-localize with p53 and forms a distinctive web-like structure in the nucleus (Supplementary Fig. 13). We show that E4-ORF3 demarcates the formation of *de novo* H3K9me3 heterochromatin domains in ΔE1B-55k-infected cells. E4-ORF3 is, for the most part, adjacent to H3K9me3, indicating it acts as a novel platform that catalyses heterochromatin formation through transient or long-range interactions (Supplementary Figs 25–27). Using high-resolution confocal microscopy, we show that E4-ORF3 forms a continuous scaffold that specifies *de novo* heterochromatin assembly as it weaves through the nucleus (Fig. 4b). These data demonstrate a direct role for E4-ORF3 in orchestrating H3K9me3 heterochromatin silencing at p53 target promoters. Furthermore, they reveal an extraordinary nuclear scaffold that either builds on existing architectural features that organize cellular DNA or is a novel viral construction that targets heterochromatin assembly at p53 target promoters.

### Selective silencing of the p53 transcription program

These data beg the question as to the specificity of E4-ORF3 in silencing p53 targets. To determine the global consequences on cellular transcription, we performed genome-wide expression analyses on infected SAECs (Supplementary Figs 28 and 29). These studies demonstrate that E4-ORF3 is an exclusive player in the global transcriptional changes induced upon viral infection. There are 1,730 overlapping genes that are similarly up or downregulated by a log-fold change

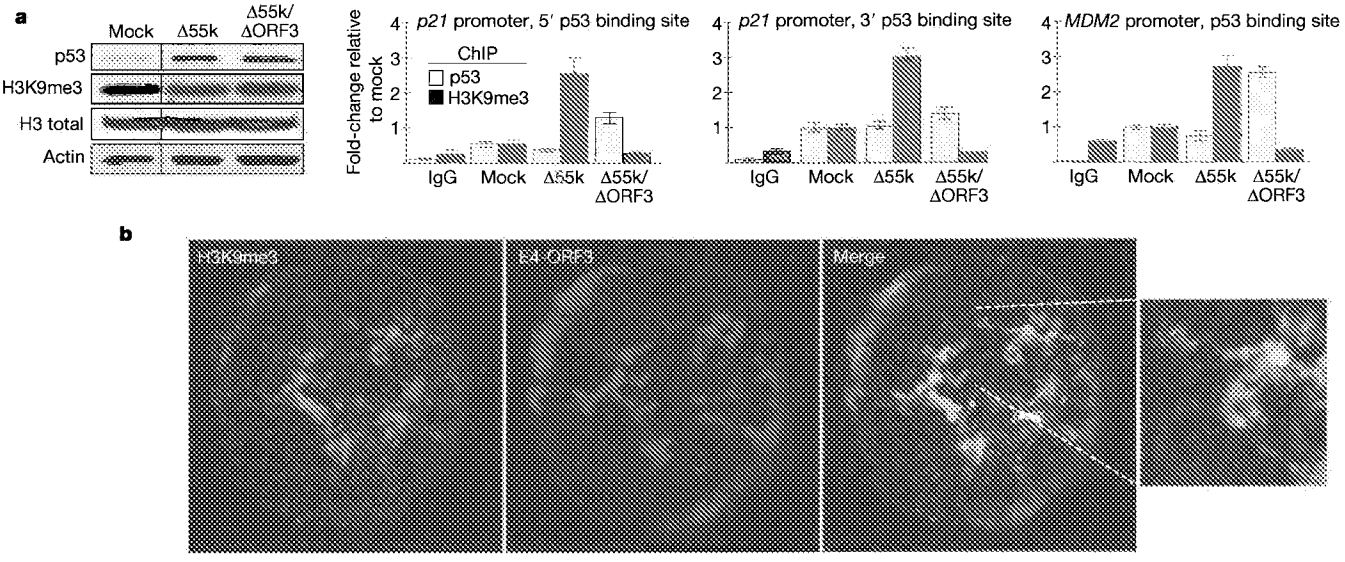


**Figure 4 | E4-ORF3 forms a nuclear scaffold that specifies heterochromatin assembly and H3K9 trimethylation at p53 target promoters. a**, Protein lysates from infected U2OS cells (36 h.p.i.) were analysed for total histone H3 or H3K9me3 levels by immunoblotting. H3K9me3 and p53 ChIPs were quantified by RT–qPCR, normalized relative to input DNA and plotted as fold-change relative to mock. Error bars represent s.d. ($n = 2$) **b**, H3K9me3 (green) and E4-ORF3 (red) localization in Δ55k-infected SAECs (36 h.p.i.) was visualized by immunofluorescence. A high resolution confocal slice (0.3 μm) through the nucleus is shown with a magnified section of E4-ORF3 and associated heterochromatin domains on the far right.

greater than two in both ΔE1B-55k and ΔE1B-55k/ΔE4-ORF3 versus mock, which reflect a common transcriptional program (Fig. 5a). These global changes are associated with the cell cycle and E2F activation (Supplementary Tables 1 and 2). This is consistent with E1A-mediated inactivation of RB[34] and recruitment of p300 and PCAF (also known as EP300 and KAT2B, respectively) to induce active histone acetylation marks at the promoters of genes involved in cell growth, division and DNA synthesis[35,36]. Thus, E4-ORF3-induced heterochromatin silencing, as well as the scaffold it forms throughout the nucleus, does not affect the global activation of cellular transcripts induced by viral infection.

To define the genes specifically targeted by E4-ORF3, we compared ΔE1B-55k/ΔE4-ORF3- versus ΔE1B-55k-infected cells. E4-ORF3 prevents the transcriptional activation of 265 genes by a log-fold change of two or more in ΔE1B-55k-infected cells. To determine how many of these genes are likely to be regulated by p53, we used two criteria: the presence of consensus p53–DNA binding sites in their promoters and their induction upon treatment with the MDM2 antagonist, nutlin. A heat map of top transcripts differentially upregulated in response to ΔE1B-55k/ΔE4-ORF3 and nutlin includes well known p53 targets (*MDM2, FAS, PIG3, TP53INP1, BTG2, LRDD*) associated with growth inhibition and apoptosis, as well as novel targets (*HRH1, RNASE7, JMJD1C*) (Fig. 5b and Supplementary Fig. 30). Of the 265 differentially upregulated genes, 73% are induced in response to nutlin and/or have predicted p53 binding sites (Fig. 5c and Supplementary Tables 3, 4). A pathway analysis of E4-ORF3-regulated transcripts indicates that, in addition to the p53 pathway, there is a significant over-representation of genes associated with immune modulation as well as tissue/vascular remodelling (Supplementary Table 5). These data indicate that E4-ORF3 may target p53 promoters as part of a general anti-viral transcriptional silencing program, which is consistent with the highly defective replication of ΔE1B-55k/ΔE4-ORF3 in primary cells (Supplementary Fig. 31).

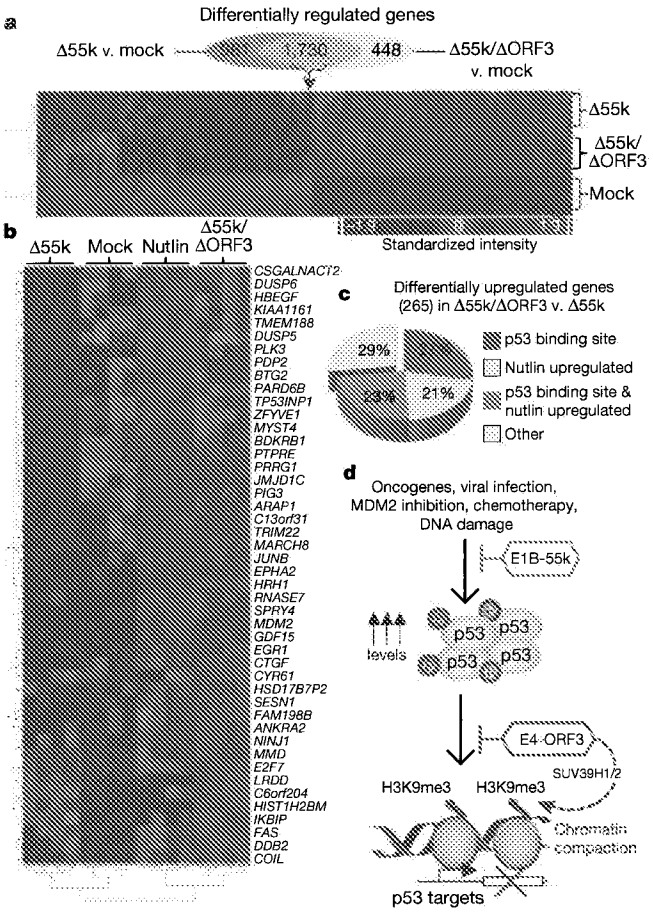


**Figure 5 | p53 transcriptional targets are silenced selectively in the backdrop of global transcriptional changes that drive oncogenic cellular and viral replication.** Affymetrix global gene expression analyses of SAECs. **a**, Heat map of the 1,730 overlapping differentially regulated genes (log-fold change >2 or <−2 with a false discovery rate (FDR) of 0.05) between Δ55k/ΔORF3- and Δ55k- versus mock-infected SAECs (36 h.p.i.). **b**, Unsupervised hierarchical clustering of 46 top differentially upregulated transcripts in both Δ55k/ΔORF3 infection and nutlin treatment. **c**, Pie-chart depicting the percentage of upregulated transcripts (log-fold change >2 and FDR of 0.05) in Δ55k/ΔORF3 versus Δ55k that have predicted p53 transcription factor binding sites and/or induced by a log-fold change >1.5 in response to nutlin. **d**, Summary and model.

## Discussion and perspective

The conclusions of our study challenge the general assumption that p53 induction and phosphorylation is tantamount to p53 activity, which is the premise for several cancer therapies[11–13]. Our data reveal a novel and dominant mechanism of p53 inactivation that acts through the targeted epigenetic silencing of p53 target promoters. We identify a viral protein, E4-ORF3, which seems to form a novel scaffold that weaves through the nucleus, directing SUV39H1/2 H3K9me3 heterochromatin assembly at p53 target promoters to silence p53-activated transcription in response to genotoxic and oncogenic stress (Fig. 5d). Remarkably, this suppressive nuclear web selectively ensnares p53 and anti-viral genes while operating in the backdrop of global transcriptional changes that drive pathological cellular and viral replication.

There is a profound functional overlap between adenovirus early proteins and tumour mutations[37]. Thus, a major question is if E4-ORF3 reflects or exhorts an existing cellular mechanism and nuclear structure that censors p53 transcriptional activity. Strikingly, all of the known targets of E4-ORF3, PML[38], the MRE11/RAD50/NBS1 (NBS1 is also known as NBN) (MRN) DNA damage/repair complex[39] and Tif1α[40] (also known as TRIM24) are subverted by tumour mutations. It is intriguing to speculate that E4-ORF3 physically integrates the inhibitory effects of several cancer pathway mutations, both known and yet to be discovered, which together have emergent functions[4] in silencing p53 activity. Similar to the discovery of p53 with a viral protein[2,3], E4-ORF3 provides a powerful dynamic probe with which to define critical cellular factors that induce *de novo* epigenetic silencing of p53 target promoters in somatic cells. This has important implications for understanding how high levels of wild-type p53 might also be inactivated in cancer as well as the dynamic mechanisms that induce aberrant epigenetic silencing of tumour-suppressor gene loci. Finally, our identification of E4-ORF3 changes the fundamental definition of how p53 is inactivated in adenovirus-infected cells, which is a critical mechanistic insight that could now enable the rational development of true p53 tumour-selective adenoviral therapies.

## METHODS SUMMARY

Cells were grown and infected with established conditions[21,22]. Protein lysates were analysed by western blotting[21,22]. Quantitative polymerase chain reaction with reverse transcription (RT–qPCR) was used to quantify p53 targets[21], and normalized relative to 18S. For luciferase assays, U2OS cells were transfected and infected after 36 h. D-Luciferin (100 μM) was added 4 h post-infection (h.p.i.) and luminescence quantified every hour. Global gene expression was determined using Affymetrix Human Exon 1.0ST arrays and analysed with Partek and Genomatix software.

**Full Methods** and any associated references are available in the online version of the paper at www.nature.com/nature.

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**Author Contributions** C.S. performed the p53 activation and virus studies, including immunoblotting, RT–qPCR and microarray experiments. F.E.E. performed all chromatin immunoprecipitation and immunofluorescence studies. K.C.E. performed the luciferase assays, E4-ORF3 sufficiency and complementation, and assisted C.S. with viral mutant studies. C.C.O. analysed the array data and wrote the paper with contributions from all authors. C.C.O. was responsible for the overall conceptual design and supervision of the studies.

**Author information** Microarray data are deposited in NCBI's Gene Expression Omnibus (GSE20607). Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at www.nature.com/nature. Correspondence and requests for materials should be addressed to C.C.O. (oshea@salk.edu).

## METHODS

**Cells, growth conditions and viral infections.** Primary human cells from multiple donors were obtained from Cambrex/Lonza, which were grown and infected as described previously[21,22]. Multiplicities of infection (m.o.i.) were determined experimentally. U2OS, H1299-D1, MDA-MB-231, HCT-116, C33A and A549 cells were infected at a m.o.i. of 30, and SAECs, HMEC and HBEC at a m.o.i. of 10. U2OS cells with an IPTG-inducible *ARF*[41] were a kind gift from G. Peter's laboratory. H1299-D1 is a stable cell line that expresses a *p53* cDNA construct under the control of a ponasterone-inducible promoter. To induce p53 expression, cells were treated 5 h before infection with 5 μM ponasterone A (Invitrogen), which was re-added at the time of infection.

**Viruses and viral replication assays.** Viral replication and titres were quantified by secondary infection of 293/E4/pIX cells using an ELISA assay with a rabbit anti-adenovirus type 5 antibody (Abcam) at 1:1,000, as described previously[21,22,42]. Mock infection was performed with the E1-deleted non-replicating adenovirus *dl*312 (ref. 43). Wild-type virus is WtD[18], ΔE1B-55k (Δ55k) is *dl*1520/ONYX-015 (refs 13, 18). The ΔE1B-55k/ΔE4-ORF3 (Δ55k/ΔORF3) virus, *dl*3112, has an identical genome backbone to *dl*1520/ONYX-015 but has a single base pair deletion (nucleotide 7143r) that ablates E4-ORF3 expression[44]. ΔE4 is *dl*366 which has a deletion that ablates the E4 genes[45]. ΔE1B-55k/ΔE4-ORF6 (Δ55k/ΔORF6) is *dl*367 which has mutations that ablate both E1B-55k and E4-ORF6 (ref 46). ΔORF3 is E4inORF3 (ref. 47). ΔE1B-55k/ΔE1A-13s (Δ55k/Δ13s) has an E1B-55k gene deletion and mutation that ablates the 13s splice form of E1A[48]. ΔE1B-55k/E1AΔp300 (Δ55k/E1AΔp300) has an E1B-55k deletion and E1A point mutation that abrogates E1A–p300 binding[21,48]. Ad-CMV E1-deleted replication-incompetent adenovirus vectors (Ad-CMV-Dest, Invitrogen) were constructed to express either E4-ORF3 (Ad-ORF3) or GFP (Ad-GFP).

**Plasmids, drugs and DNA damage.** pDONR221 plasmid for SUV39H1 was purchased from the Harvard Institute of Proteomics (Plasmid ID: HsCD00044660) and cloned into a CMV expression vector in frame with an N-terminal myc tag. Doxorubicin (dox, Sigma) at 0.5 μg ml$^{-1}$ for 12 h was used as a positive control for p53 activation. 5-fluorouracil (Sigma) was used at 50 μg ml$^{-1}$, TSA (Sigma) at 5 μM and nutlin-3 (Calbiochem) at 10 μM. γ irradiation was performed via exposure to a cobalt-60 source.

**Protein lysates and western blot analysis.** Protein lysates were harvested, normalized and analysed as described previously[21,22]. Primary antibodies were from Santa Cruz Biotechnology (p53 DO-1 and FL393, GFP, MDM2 N20), Cell Signaling Technology (phospho-p53 serine (Ser) 6, 9, 15 (16G8), 20, 33, 46, 315, 392 and threonine (Thr) 81), Upstate (p21), Calbiochem (p53 PAb1620 and 240, MDM2 2A10), Abcam (actin and histone H3), Active Motif (H3K9), Ascenion (E4-ORF3 (6A11)), ARF[21], and E1B-55k (2A6). Actin expression was used as a loading control. Primary antibodies were detected with secondary antibodies labelled with either IRDye800 (Rockland), Alexa Fluor 680 (Molecular Probes) or horseradish peroxidase-conjugated secondary antibodies. Fluorescent antibodies were visualized using a LI-COR-Odyssey scanner and horseradish peroxidase antibodies with ECL chemiluminescence followed by autoradiography.

**RT–qPCR analysis.** RT–qPCR quantification of p53 transcriptional targets was performed using an ABI Prism 7900 system, as described previously[21]. Total RNA (1 μg) was reverse-transcribed with Applied Biosystems' High Capacity Reverse Transcription. RT–qPCR reactions were set up using Taqman Fast mix (ABI), and run in triplicate. Input cDNA (10 ng) was used for 18S analysis, and 50 ng of input cDNA was used for all other targets. All samples were normalized to 18S expression.

**Immunofluorescence.** Cells were fixed in 4% paraformaldehyde and stained as described previously[21,22]. Primary antibodies were from Santa Cruz Biotechnology (p53 DO-1 and FL393, SUV39H2 Z-23), Cell Signaling Technology (SETDB1/ESET, G9a/EHMT2), Diagenode (H3K9me3 mouse), Active Motif (H3K9me3 rabbit), Abcam (SUV39H2, SUV39H1), and E1A (M73), Roche (myc 9E10), and Ascenion (E4-ORF3 (6A11)). Alexa 488-, 555- and 633-conjugated secondary antibodies (Molecular Probes) were used for detection of primary antibodies. Images were acquired with a Zeiss Axioplan2 imaging system (Supplementary Figs 2a, 13, 17 and 20), a Nikon A1 laser confocal system (Figs 3d, e, 4b and Supplementary Figs 21, 25 and 26) and a Leica confocal SP2 (Supplementary Figs 18, 19 and 27). Pictures were edited in Adobe Photoshop. Background was corrected using same grey level values for all channels to remove noise, except for reducing the contrast of SETDB1 staining for the Δ55k/ΔORF3 panel in Supplementary Fig. 21. The raw microscope images acquired with the Nikon A1 laser confocal system were filtered with a 5 kernel median filter.

**Real-time luciferase assays.** U2OS cells were reverse-transfected with luciferase reporter plasmids, p53-luc, p53-mutant and pGL3 (Stratagene) using FuGENE 6 (Roche). After 36 h, cells were infected with viruses. After 4 h, medium was replaced by high-glucose Dulbecco's modified Eagle's medium without phenol red, supplemented with 15 mM HEPES pH 7.4 (Gibco) and 100 μM D-luciferin (BIOSYNTH Chemistry & Biology). Plates were sealed with vacuum grease (Dow Corning) and custom-made glass cover slips. Luciferase activity was analysed using the temperature-controlled Safire II plate reader with Magellan 6 software (Tecan Group). The luminescence for each well was integrated over 4 s and read at 1 h intervals for 48 h at a temperature setting of 37 °C. Data was graphed in Excel 2007 (Microsoft) by plotting the average luminescence of the triplicates at each time point.

**Chromatin immunoprecipitation assays.** p53 and H3K9me3 chromatin immunoprecipitations (ChIPs) were performed as described previously[25,49]. Cells were fixed with 1% formaldehyde for 15 min and stopped with 0.125 M glycine, lysed in Szak's modified RIPA buffer or 1% SDS lysis buffer and sonicated to shear genomic DNA. p53 and H3K9me3 ChIPs were performed using 2 μg of p53 DO-1 monoclonal antibody and 5 μl of anti-H3K9me3 rabbit serum (Active Motif), respectively. A mouse IgG isotype control and non-immune rabbit serum were used as controls for specificity. Immuno-complexes were isolated using Protein G (mouse antibodies) or Protein A beads (rabbit antibodies). Crosslinking was reversed by incubating at 65 °C overnight. DNA was purified and analysed using either semiquantitative PCR or RT–qPCR using conditions and primers described previously[25,50,51]. For RT–qPCR, samples were analysed in duplicate using a Sybr GreenER mix (Invitrogen) and quantified on a MyiQ RT–qPCR machine (Bio-Rad). A tenfold dilution series of input DNA was used to determine the efficiency of the PCR for each primer set. ChIP DNA samples were normalized relative to their respective input DNAs.

**Affymetrix expression arrays and data analysis.** Human primary quiescent SAECs were infected and harvested at 36 h.p.i. All samples were done in duplicate, and corresponding lysates were western-blotted. Total RNA was isolated and purified using TRIzol with the PureLink RNA Mini kit (Invitrogen), and treated with DNase I (Ambion). Total RNA (100 ng), spiked with Poly-A controls, was used to synthesize cDNA, according to recommended protocols using the Ambion WT Expression kit. Fragmentation and labelling of cDNA was performed as per the Affymetrix GeneChip WT Terminal Labeling standard protocol. Samples were hybridized to Affymetrix Human Exon 1.0ST arrays, washed, stained and scanned with the Affymetrix GCS 3000 7G and GeneChip Operating Software v1.3 to produce .CEL intensity files. Quality control analysis of all chips was performed with the Affymetrix expression console.

All array data were analysed using tools in the Partek Genomic Suite of software (Partek)[52]. Exon-level data were imported and filtered to include only those probes that are in the 'Core Meta-probeset', which represents 17,800 RefSeq genes and full-length GenBank mRNAs. A pre-background adjustment was performed for GC content followed by robust multi-array analysis (RMA) background correction, quantile normalization and mean probeset summarization[53,54] (Supplementary Fig. 29). Sources of variation due to random experimental factors, such as scan date and experiment were batch-removed using analysis of variance (ANOVA). The fold-change and *p*-values for differentially expressed genes between Δ55k/ΔORF3 versus mock, Δ55k versus mock, Δ55k/ΔORF3 versus Δ55k and nutlin versus mock were determined using linear contrasts in a one-way ANOVA model using method of moments[52]. The ANOVA model used was:

$$Y_{ij} = \mu + \text{virus/treatment}_i + \varepsilon_{ij},$$

where $Y_{ij}$ represents the $j$th observation on the $i$th virus/treatment, $\mu$ is the common effect for the whole experiment and $\varepsilon_{ij}$ represents the random error present in the $j$th observation on the $i$th virus/treatment. The errors $\varepsilon_{ij}$ are assumed to be normally and independently distributed with mean 0 and standard deviation $\sigma$ for all measurements. A step-up false discovery rate (FDR) of 0.05 was applied to *p*-values calculated by ANOVA as the cut-off for significant differentially expressed genes.

Differentially expressed genes were analysed using the Genomatix Pathway System (GePS) and GeneRanker programs, which uses information extracted from public and proprietary databases. Over-representation of different biological terms (Gene Ontology categories, signal transduction pathways) within the input gene list are calculated and listed together with their respective *p*-value[55]. Signal Transduction Pathway Associations are obtained by Genomatix with a proprietary literature data mining algorithm based on all available Pubmed abstracts.

**Promoter analysis.** Genomatix Gene2Promoter was used to retrieve the optimized promoters of the 265 differentially upregulated transcripts in Δ55k/ΔORF3- versus Δ55k-infected SAECs and filter them for p53 transcription factor binding sites (TFBS) using MatInspector[56]. MatInspector searches transcription factor matrix matches based on position weight matrices[57], which has been used successfully to detect functional p53 transcription factor elements[58]. Six different matrices for p53 were used as described in Supplementary Table 4. Default

matrix indices (core similarity: 0.75; matrix similarity: optimized) were set during TFBS searching. The "core sequence" of a matrix is defined as the (usually 4) consecutive highest conserved positions of the matrix. The maximum core similarity of 1.0 is only reached when the highest conserved bases of a matrix match exactly in the sequence. The matrix similarity score takes into account all bases over the whole matrix length. A perfect match gets a score of 1.00, a "good" match to the matrix usually has a similarity of >0.80.


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**Name:** **Frank McCormick, PhD, FRS, DSc (Hon)**

Position: Director, UCSF Helen Diller Family Comprehensive Cancer Center
E. Dixon Heise Distinguished Professor in Oncology
David A. Wood Distinguished Professor of Tumor Biology and Cancer Research

Associate Dean, School of Medicine

Distinguished Professor in Residence, Department of Microbiology and Immunology
Distinguished Professor in Residence, Department of Biochemistry and Biophysics

Address: UCSF Helen Diller Family Comprehensive Cancer Center
1450 3rd Street, Room HD-371, UCSF Box 0128
San Francisco, CA 94158-9001

Voice: 415-502-1710
Fax: 415-502-1712
E-mail: mccormick@cc.ucsf.edu
www: http://cancer.ucsf.edu/

## EDUCATION:

| | | | |
|---|---|---|---|
| 1968-72 | University of Birmingham, England, UK | B.Sc. | Biochemistry |
| 1972-75 | University of Cambridge, England, UK | Ph.D. | Biochemistry |

## LICENSES, CERTIFICATION:

Not Applicable

## PRINCIPAL POSITIONS HELD:

| | | | |
|---|---|---|---|
| 1975-1978 | State University of New York at Stony Brook | Fellow | Prof. Seymour S. Cohen |
| 1978-1981 | Imperial Cancer Research Fund, London | Fellow | Dr. Alan Smith |
| 1981-1990 | Cetus Corporation | | Director of Molecular Biology |
| 1990-1991 | Cetus Corporation | | Vice President, Research |
| 1991-1992 | Chiron Corporation | | Vice President, Research |
| 1992-1996 | Onyx Pharmaceuticals | | Founder, Chief Scientific Officer |
| 1997-now | University of California, San Francisco<br>Helen Diller Family Comprehensive Cancer Center and Cancer Research Institute | | Director |
| 1997-now | University of California, San Francisco, School of Medicine | | Associate Dean |
| 1997-now | University of California, San Francisco, Department of Microbiology and Immunology | | Professor |

**HONORS AND AWARDS:**

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|---|---|
| 1996 | Fellow of the Royal Society |
| 2002 | Bristol Myers Squibb Unrestricted Cancer Research Grant |
| 2002 | AACR – G.H.A. Clowes Memorial Award |
| 2002 | Novartis Drew Award in Biomedical Research |
| 2003 | University of Chicago, Cancer Research Center, Shubitz Award |
| 2004 | Nomination, Alfred P. Sloan, Jr. Prize, General Motors Cancer Research Foundation |
| 2005 | Institute of Medicine |
| 2008 | Salute to Excellence Award, American Liver Foundation |
| 2008 | Honorary Degree, Doctor of Science, University of Birmingham, England, UK |
| 2010 | ASCO Science of Oncology Award |

**KEYWORDS/AREAS OF INTEREST:**

Cancer, virology, Ras, p53, oncogenes, tumor suppressors, breast cancer, neurofibromatosis, protein kinases

**PROFESSIONAL ACTIVITIES:**

**PROFESSIONAL ORGANIZATIONS**

**Memberships**

| | |
|---|---|
| 1997-now | American Association for Cancer Research |
| 1997-now | American Society for Microbiology |
| 1998-now | American Association for the Advancement of Science |
| 1998-now | American Society of Gene Therapy |
| 2005-now | Institute of Medicine |
| 2008-now | American Society of Clinical Oncology |

**Service to Professional Organizations**

| | | |
|---|---|---|
| 1997-2003 | ONYX Pharmaceuticals | Scientific Advisory Board |
| 1998-1999 | NCI Developmental Therapeutics Program | Scientific Advisory Board |
| 1998-2003 | NCI Board of Scientific Counselors | Advisory Committee |
| 1998-2001 | ICONIX Pharmaceuticals | Scientific Advisory Board |
| 1998-2004 | The Jackson Laboratory Bar Harbor, Maine | Scientific Advisory Board |
| 1998-2007 | Friedrich Miescher-Institut | External Advisory Board |
| 2000-now | Van Andel Institute | Scientific Advisory Board |
| 2001-2002 | Sagres | Scientific Advisory Board |
| 2001-now | University of Wisconsin Comprehensive Cancer Center | External Advisory Board |
| 2002-2005 | American Association of Cancer Research | Board of Directors |
| 2002-2006 | Alberta Cancer Board | Advisory Committee on Research |
| 2002-2007 | Alliance for Cancer Gene Therapy | Scientific Advisory Council |
| 2003-2006 | Association of American Cancer Institutes | Board of Directors |
| 2003-2010 | Memorial Sloan-Kettering Cancer Center | Board of Scientific Consultants |
| 2003-now | Exelixis, Inc | Board of Directors |
| 2003-now | NCI Initiative for Chemical Genetics | External Review Committee |
| 2003-2008 | Nexgenix Pharmaceuticals, LLC | Scientific Advisory Board |
| 2004-2009 | Emory Winship Cancer Institute | External Advisory Board |
| 2004-now | Canary Foundation | Scientific Advisory Board |
| 2005-2007 | Friends of Cancer Research | Scientific Advisory Board |

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|---|---|---|
| 2005-2007 | UT Southwestern Medical Center, Harold C. Simmons Comprehensive Cancer Center | External Advisory Board |
| 2005-2008 | American Association for Cancer Research | Finance Committee |
| 2005-now | Columbia University, New York, Herbert Irving Comprehensive Cancer Center | Scientific Advisory Board |
| 2005-now | Aglaia Biomedical Ventures B.V. | Scientific Advisory Board |
| 2006-2007 | Burnham Institute for Medical Research | Scientific Advisory Board |
| 2006-now | Fluidigm Corporation | Scientific Advisory Board |
| 2006-2007 | KineMatik Limited | Scientific Advisory Board |
| 2006-2008 | MannKind Corporation | Scientific Advisory Board |
| 2006-now | Melanoma Therapeutics Foundation | Board and Scientific Advisory Board |
| 2007-2008 | BiPar Sciences | Scientific Advisory Board |
| 2007-now | Daiichi-Sankyo, Ltd. | Scientific Advisory Board |
| 2008-now | TriAct Therapeutics, Inc | Scientific Advisory Board |
| 2008-now | ORCA Therapeutics, Inc | Scientific Advisory Board |
| 2008-now | Dana-Farber/Harvard Cancer Center | External Advisory Board |
| 2008-2010 | Arresto Biosciences | Board of Directors |
| 2008-now | Life Sciences Institute | Scientific Advisory Board |
| 2009-now | Van Andel Institute | Faculty Committee Review |
| 2009-now | Dicerna | Scientific Advisory Board |
| 2009-now | Jennerex Biotherapeutics, Inc. | Scientific Advisory Board |
| 2010-now | Aduro BioTech | Board of Directors and Scientific Advisory Board |
| 2010-now | Duke University | Scientific Advisory Board |
| 2010-now | Portola Pharmaceuticals | Translational Advisory Board |

**Organizing Committees:**

| | | |
|---|---|---|
| 2001 | AACR Program Committee 93rd Annual Meeting | Co-Chair |
| 2003 | Gordon Research Conference, Molecular Therapeutics of Cancer Queen's College, Oxford, UK | Vice-Chair |
| 2003 | AACR, Nominating Committee for the Laboratory Research Awards and Professorship | Member |
| 2004 | Gordon Research Conference, Molecular Therapeutics of Cancer Colby Sawyer College, New Hampshire | Chair |
| 2004 | AACR, Nominating Committee for the Laboratory Research Awards and Professorship | Member |
| 2004 | AACI, Annual Meeting Program Committee | Chair |
| 2005 | Keystone Symposium, Molecular Targets for Cancer Therapy | Co-Chair |
| 2005 | AACR Award for Lifetime Achievement in Cancer Research Selection Committee | Chair |
| 2006 | AACR Major Scientific Symposium: MEK Inhibitors and Target Ras Pathways | Chair |
| 2006 | Nature-Centro Nacional de Investigaciones Oncologicas (CNIO) International Conference: Oncogenes and Human Cancer: The Next 25 Years, Scientific Organizing Committee | Member |
| 2007 | AACR-Eli Lilly Team Science Award Selection Committee | Chair |
| 2007 | AACR-NCI-EORTC Scientific Committee | Member |
| 2007 | Netherlands Genomics Initiative: Cancer Genomics Center Workshop Organizing Committee | Member |
| 2010 | AACR Program Committee 101st Annual Meeting | Chair |
| 2010 | AACR Task Force of Co-development of Investigational Drugs | Chair |

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| 2010 | AACR Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research | Member |

**SERVICE TO PROFESSIONAL PUBLICATIONS**

**Editorial Boards:**

| | |
|---|---|
| 1991-now | Cell Growth and Differentiation |
| 1995-1998 | Molecular and Cellular Biology |
| 1996-now | BBA Reviews on Cancer-Elsevier |
| 1998-now | Neoplasia |
| 2001-now | Cancer Cell |
| 2002-2007 | Molecular Cancer Research (Senior Editor) |
| 2003-2007 | Journal of Molecular Medicine (U.S. Editor-in-Chief) |

**Ad hoc Reviewing:**

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|---|---|
| 1997 | Cancer Research, Nature, Oncogene, Science |
| 1998 | Cancer Research, Clinical Cancer Research, EMBO, Grant Review for Human Frontier Science Program Organization, Nature Medicine, News & Views, Oncogene, PNAS, Science, Structural Nature |
| 1999 | American Heart Association Circulation Research Journal, Biochemistry, Blood Journal, Dutch Cancer Society, FASEB Journal, Human Gene Therapy, Journal of Clinical Investigation, Molecular Microbiology, National Academy of Sciences, Nature, Nature Oncology Research, Science, Tumor Targeting, Nature Medicine |
| 2000 | Cancer Research, Cell Biology International, Clinical Cancer Research, Gene and Development, Journal of Clinical Oncology, National Academy of Sciences, Nature Biotechnology, Nature Medicine, PNAS, Science |
| 2001 | British Journal of Cancer, Cancer Research, EMBO, Journal of Molecular Biology, Journal of Virology, Nature Cell Biology, Nature Structural Biology, Nature Medicine, Science, Structure, Oncology |
| 2002 | Cancer Research, Cell Biochemistry and Biophysics, Journal of Clinical Investigation, Journal of Clinical Oncology, Journal of Virology, Proceedings of the National Academy of Sciences, Nature Biotechnology, Nature Medicine |
| 2003 | The Cancer Journal |
| 2007 | BMC-series Journal, Oncogene |
| 2008 | Oncogene, PNAS |

**INVITED PRESENTATIONS:**

**INTERNATIONAL:**

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|---|---|
| 2002 | Faculty of Medicine, Department of Biochemistry and Molecular Biology, University of Calgary, Calgary, Canada, Robert B. Church Lecturer in Biotechnology 2001 |
| 2002 | "A Century Colloquium", Imperial Cancer Research Fund, University of Warwick, England, UK. |
| 2003 | MRC Cancer Cell Unit, Hutchison/MRC Research Centre, Cambridge, England, UK. |
| 2003 | Keystone Symposium on Molecular and Cellular Biology, "Cancer Therapy Based on the p53 Pathway", Banff, Alberta, Canada. |
| 2003 | Ontario Regional Cancer Centre, "Oncolytic Viruses as Cancer Therapeutics", Banff, Alberta, Canada. |
| 2003 | Max-Planck-Institut fur Molekulare Physiologie, Annual Retreat, Ringberg, Bavaria, Germany. |

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| 2003 | Beatson International Cancer Conference, Keynote Speaker, Cell Signaling and Cancer Conference, Cancer Research UK, Glasgow, Scotland, UK. |
| 2003 | The Institute of Cancer Research, The Royal Marsden Tenth Annual Link Lecture, Royal Cancer Hospital, Surrey and London, England, UK. |
| 2003 | European Molecular Biology Organization/Federation of European Biochemical Societies, Molecular Mechanisms in Signal Transduction, Spetses, Greece. |
| 2003 | The 41st Annual Meeting of Japan Society of Clinical Oncology, Sapporo, Japan. |
| 2003 | Alberta Cancer Board Annual Research Meeting, Banff, Alberta, Canada. |
| 2004 | 90th Annual Meeting of the Japan Society of Gastroenterology, "The Front Line of Cancer Therapy", Sendai, Japan. |
| 2004 | Fondation des Treilles, "New Anti-Cancer Approaches Based on our Molecular Understanding of Oncogenesis", Tourtour, France. |
| 2004 | University of Warwick, Genes and Cancer 2004, 21st Meeting, Warwick, England, UK. |
| 2004 | Canadian Institutes of Health Research, Institute of Genetics and Institute of Cancer Research, Third Annual Investigators Meeting, Jackson Point, Ontario, Canada. |
| 2004 | Molecular Biology/Signal Transduction Seminar, McMaster University, Hamilton, Ontario, Canada. |
| 2005 | Biomedical Research Council Distinguished Visitor, Singapore. |
| 2005 | The 8th Annual New England Biolabs Symposium on Molecular and Cellular Biology New England Biolabs, Pickering, Ontario, Canada. |
| 2005 | Cancer Genomics Center, Genomic Approaches and Molecular Mechanisms in Cancer, Royal Tropical Institute, Amsterdam, The Netherlands. |
| 2006 | 9th Cancer Research UK Beatson International Cancer Conference: 24 Years of Ras and Human Cancer, Caledonian University, Glasgow, Scotland, UK. |
| 2007 | British Columbia Cancer Research Centre, 2007 Richard T. Israels QC Memorial Lecture; Vancouver, British Columbia, Canada. |
| 2007 | The National Cancer Research Institute Cancer Conference, Birmingham, England, UK. |
| 2007 | Nature/CNIO (Centro Nacional de Investigaciones) Conference: "Oncogenes and Human Cancer: The Next 25 Years," Madrid, Spain. |
| 2007 | Cancer Genomics Centre Workshop, "GEFs and GAPs as therapeutic targets." Utrecht, The Netherlands. |
| 2007 | Daiichi-Sankyo, Ltd., Tokyo, Japan. |
| 2008 | Daiichi-Sankyo, Ltd., Tokyo, Japan. |
| 2008 | Novartis Oncology LEAD Summit VI, Montreal, Canada. |

2009 Gairdner-Alberta Cancer Research Institute Symposium: "Research Advances in Our Understanding of the Biology and Treatment of Cancer," Edmonton, Alberta, Canada

2009 FEBS/EACR Advanced Lecture Course, "Molecular Mechanisms in Signal Transduction and Cancer", Spetses, Greece

2009 CNIO-Centro Nacional de Investigaciones Oncológicas: "Targeting the Ras Pathway", Madrid, Spain

2010 Institute of Predictive and Personalized Medicine of Cancer, Barcelona, Spain

2010 Vienna Biocenter Seminar, Vienna, Austria

2010 Cancer Genomics Centre / Centre for Biomedical Genetics Conference: "Molecular Mechanisms in Cancer," Amsterdam, The Netherlands

2010 Mitchell Lecture, Queen's University, Belfast, Ireland

2011 Lorne Cancer Conference, Lorne, Australia

**NATIONAL:**

1998 AACR, Molecular Biology and Pathology of Neoplasia, The Edward A. Smuckler Memorial Workshop, Keystone, CO

2002 University of Texas M. D. Anderson Cancer Center's 43rd Annual Clinical Conference "Drug Discovery and Clinical Evaluation in the 21st Century", Houston, TX.

2002 Cellular and Molecular Medicine, Graduate Training Program, School of Medicine, Johns Hopkins University, CMM Distinguished Lecture Series, Baltimore, MD.

2002 Harvard Center for Cancer Biology, Harvard Medical School, Harvard University, Distinguished Lecture Series, Boston, MA.

2002 Cold Spring Harbor Laboratory, Seminar Series, Cold Spring Harbor, NY.

2002 American Society of Clinical Oncology, Special ASCO Media Event: Meet the Expert, "Unlocking Cancer's Secrets: New Pathways to Targeted Treatments", New York, NY.

2002 Chicago Biological Signal Transduction Symposium 2002, Northwestern University Medical School, Chicago, IL.

2002 NNFF Consortium for the Molecular Biology of NF1 and NF2, "Tumorigenesis", Aspen, CO.

2002 2002 Rockefeller University Cancer Symposium, "A Vision for the Future: Molecular Approaches to Cancer Therapy", New York, NY.

2002 Gordon Research Conference on Chemotherapy of Experimental and Clinical Cancer, Bristol-Myers Squibb Pharmaceutical Research Institute. Colby-Sawyer College, New London, NH.

2002 University of Pittsburgh, Department of Biological Sciences, Pittsburgh, PA.

2002 University of Colorado, Cellular and Structural Biology, Health Sciences Center, School of Medicine, "Cells, Development and Cancer" Seminar Series, Denver, CO.

2003 Beth Israel Deaconess Medical Center and Harvard Medical School, Combined Grand Rounds, Department of Pathology and Division of Cancer Biology and Angiogenesis, Boston, MA.

2003 The University of Chicago, Cancer Research Foundation, Simon M. Shubitz Award Lecture, Chicago, IL.

2003 University of Washington, Biochemistry Department Graduate Student Seminar Series, Seattle, WA.

2003 National Institute of Health, National Cancer Institute, Critical Molecular Pathways Retreat, Wye River Conference Center, Queenstown, MD.

2003 Eli Lilly Cancer Discovery Research Seminar, Indianapolis, IN.

2003 Medical College of Georgia, Program in Molecular Medicine and Genetics, Augusta, GA.

2004 AACR/Japanese Cancer Association Joint Conference, Advances in Cancer Research, Waikoloa, HI.

2004 2004 Robert Sternlicht Lecture in Pharmacology and Hematology/Oncology, Case Western Reserve University, Cleveland, OH.

2004 Molecular and Cellular Basis of Disease Seminar, Cancer and Research Treatment Center, Department of Pathology, University of New Mexico, School of Medicine, Albuquerque, NM.

2004 "Meet the Expert" Sunrise Session, Progress in Oncolytic Viral Therapy, 95th Annual Meeting of the American Association for Cancer Research, Orlando, FL.

2004 National Institutes of Environmental Health Science, NIEHS, Martin Rodbell Memorial Lecture, Raleigh, NC.

2004 Vanderbilt University, Dept of Biochemistry, Vanderbilt-Ingram Cancer Center Research Education, Nashville, TN.

2004 The Foundation for Advanced Cancer Studies, Inc., 20th Annual Meeting on Oncogenes, Special Symposium, "New Therapeutics and Technologies", Hood College, Frederick, MD.

2004 Eli Lilly Cancer Discovery Research Seminar, Indianapolis, IN.

2004 The University of Texas M. D. Anderson Cancer Center, Blaffer Seminar Series, Department of Neuro-Oncology, Houston, TX.

2004 Cold Spring Harbor Laboratory, Keynote Speaker, Cancer Genetics & Tumor Suppressor Genes, Cold Spring Harbor, NY.

2004 University of Cincinnati Cancer Center Lecture Series, Department of Cell Biology, Neurobiology and Anatomy, Cincinnati, OH.

2004 Sideman Cancer Center, Barnes-Jewish Hospital, Washington University School of Medicine, Basic Science Seminar Series, St. Louis, MO.

2004 AACI, AACR, ASCO Joint Retreat, "Designing a Smart Clinical Trials System for the 21st Century: Optimizing the Interaction of Basic and Clinical Science," Lansdowne, VA.

2004 St. Jude Children's Research Hospital, Discoveries in Cancer Biology: From Science to Medicine Seminar, Memphis, TN.

2004 Bristol-Myers Squibb Company, Freedom to Discover Colloquium, Princeton, NJ.

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| 2004 | Association of American Cancer Institutes Annual Meeting, Chicago, IL. |
| 2005 | American Gastroenterological Association, 2005 Digestive Disease Week Chicago, IL. |
| 2005 | The University of Chicago Biomedical Sciences Cluster Committee on Cancer Biology Seminar Series, Chicago, IL. |
| 2005 | Memorial Sloan-Kettering Cancer Center, Charles B. Smith Visiting Research Professor, New York, NY. |
| 2005 | The 70th Cold Harbor Spring Harbor Laboratory Symposium: Molecular Approaches to Controlling Cancer, Cold Spring Harbor, NY. |
| 2005 | MIT Center for Cancer Research, Fourth Annual Symposium, Cambridge, MA. |
| 2005 | Baylor University Medical Center, Roundtable Discussion on Viral Gene Therapy of Human Cancers, Dallas, TX. |
| 2005 | National Cancer Institute and National Human Genome Research Institute, National Institutes of Health, Toward a Comprehensive Genomic Analysis of Cancer: A Roundtable Discussion, Washington, DC. |
| 2005 | The Salk Institute for Biological Studies, 5th Salk Institute/EMBL Oncogenes and Growth Control Meeting, La Jolla, CA. |
| 2005 | University of California, San Diego Medical Center, Moores Cancer Center Targeted Therapies in Oncology Symposium, San Diego, CA. |
| 2006 | The University of Texas, M. D. Anderson Cancer Center, Deborah M. Richman Memorial Lecture, Houston, TX. |
| 2006 | Winship Cancer Institute, Drug Development & Pharmacogenomics Academy, Emory University, Atlanta, GA. |
| 2006 | Abramson Family Cancer Research Institute, University of Pennsylvania, Philadelphia, PA. |
| 2006 | American Association for Cancer Research Annual Meeting, Chairperson, Drug Targets in the MAPK Pathway Symposium, Washington, DC. |
| 2006 | 2006 Children's Tumor Foundation International Consortium for the Molecular and Cellular Biology of NF1, NF2 and Schwannomatosis, Progress: From Bench to Bedside, Aspen, CO. |
| 2006 | Bristol-Myers Squibb Company, Freedom to Discover Colloquium, Princeton, NJ. |
| 2007 | New York University Cancer Institute Seminar Series, New York, NY. |
| 2007 | Penn State Cancer Institute, 7th Annual Rod and Ceil Mortel Visiting Scholar in Cancer Research Symposium, Hershey, PA. |

2007 Oregon Health & Science University, Medical Scientist Training Program Keynote Address Speaker, Portland, OR.

2007 American Association for Cancer Research Annual Meeting, Chairperson, Experimental and Molecular Therapeutics 15 Novel Agents Symposium, Los Angeles, CA.

2007 American Association for Cancer Research Annual Meeting, Cancer Biomarkers and Molecular Diagnostics Symposium Speaker, Los Angeles, CA.

2007 UCSF Department of Pediatrics 1st International Costello Syndrome Research Symposium 2007, Portland, OR.

2007 Halozyme Therapeutics, Inc., Seminar: "Success and failure of oncolytic viruses," San Diego, CA.

2007 Society for Melanoma Research, 2007 International Melanoma Congress, New York, NY.

2007 UCLA David Geffen School of Medicine, Department of Pathology and Laboratory Medicine, Seminar Series, Los Angeles, CA.

2008 Lombardi Comprehensive Cancer Center Oncology Grand Rounds,Georgetown University Medical Center, Washington, DC.

2008 Burnham Institute for Medical Research Center, Seminar Series Speaker, La Jolla, CA.

2008 The 19th Annual Cancer Progress Conference, Keynote Speaker, New York, NY.

2008 The Wistar Institute, Philadelphia, PA

2008 siRNA Consortium Spring Meeting, San Diego, CA

2008 American Association for Cancer Research Annual Meeting, Major Symposium: "Ras Signaling", San Diego, CA.

2008 City of Hope/UCSF collaboration and Team Presentation, "Ras as a Therapeutic Target", Duarte, CA.

2008 California Institute for Regenerative Medicine 2008 Cancer Stem Cells Workshop, Los Angeles, CA.

2008 Halozyme Therapeutics, Inc., On-site Collaboration Meeting, San Diego, CA.

2008 Association of American Cancer Institutes and Cancer Center Administrators Forum Annual Meeting, Invited Participant, Chicago, IL.

2009 M.D. Anderson, Invited Speaker, "Targeting the RAS Pathway", Houston, TX

2009 Kimmel Cancer Center, Grand Rounds, "Targeting the RAS Pathway", Philadelphia, PA

2009 AACR Annual Meeting, Invited Speaker, "Therapeutic Targeting the ras Pathways" and "Targeting the RAS Pathway", Denver, CO

2009 NCI/NIH/USDHHS Cancer Center Directors' Retreat, Arlington, VA

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| 2009 | City of Hope Graduate School of Biological Sciences, Commencement Speaker, Duarte, CA. |
| 2009 | 2009 Neurofibromatosis Conference, Session Chair, "Unraveling the Signaling Culture-Pathways of NF", Portland, OR |
| 2009 | Yale Cancer Center, Grand Rounds, "Targeting the RAS Pathway", Princeton, NJ |
| 2009 | Cancer Institute of New Jersey, Distinguished Lecture Seminar, "Targeting the RAS Pathway", New Brunswick, NJ |
| 2009 | Vanderbilt Institute of Chemical Biology Retreat, Keynote Speaker, "Targeting the RAS Pathway", Nashville, TN |
| 2009 | 6th Early Detection Research Network (EDRN), Scientific Workshop, "Impact of Early Detection on Targeted Therapy", Bethesda, MD |
| 2009 | The Brainstorming Event on The future of Cancer Therapy, Exelixis, Inc., Boston, MA |
| 2009 | AACI/CCAF Annual Meeting, Washington, D.C. |
| 2009 | Oncology Research and Development Symposium - Resistance to Targeted Therapies in Cancer, San Diego, CA |
| 2009 | AACR-NCI-EORTC - Molecular Targets and Cancer Therapeutics: Discovery, Biology and Clinical Applications, Boston, MA. |
| 2010 | Children's Tumor Foundation Consortium Retreat, Santa Monica, CA |
| 2010 | AACR 2010 Program Committee Meeting, Philadelphia, PA |
| 2010 | UCLA Institute for Molecular Medicine Seminar, UCLA, Los Angeles, CA |
| 2010 | Translational Cancer Research Seminar Series, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH |
| 2010 | AACR Annual Meeting, Washington, DC |
| 2010 | ASCO Annual Meeting, Science of Oncology Award, Chicago, IL |
| 2010 | AACI Clinical Research Initiative Meeting, Chicago, IL |
| 2010 | The University of Texas MD Anderson Cancer Center Grand Rounds, Houston, TX |
| 2010 | AACR Translational Cancer Research for Basic Scientists Workshop, Boston, MA |
| 2011 | Amgen Oncology Seminar Series, Thousand Oaks, CA |
| 2011 | Gordon Research Conference – "Cancer Genetics & Epigenetics," Ventura Beach, CA |

**REGIONAL AND OTHER INVITED PRESENTATIONS:**

2002 AACR - A.G.H. Clowes Memorial Award Lecture, AACR Annual Meeting, San Francisco, CA.

2002 AGA Research Symposium "Colon Cancer: APC-beta Catenin Pathway", San Francisco, CA.

2002 XIVth World Congress of Pharmacology, "Cancer Therapy Based on Ras and related proteins", San Francisco, CA.

2002 University of California, School of Medicine, Dean's Seminar Series, UCSF.

2002 University of California, Department of Biochemistry and Biophysics and the Hillblom Center for the Biology of Aging, Cancer Mini Symposium, "The War on Cancer: Where are We?" San Francisco, CA.

2002 University of California, School of Medicine Graduate Programs: Department of Biochemistry & Molecular Biology, Genetics, Cell Biology and Developmental Biology, 2002 TETRAD Scientific Conference at Granlibakken, Lake Tahoe, CA.

2003 The Seventh International Biotech Summit, Innovation and The Marketplace: New Risks, New Rewards, University of California, San Francisco, CA.

2003 Lawrence Berkeley National Laboratory, Life Sciences Division Seminar, Berkeley, CA.

2004 University of California, San Francisco, Department of Surgery, 3rd Annual Clinical Cancer Update, Lake Tahoe, CA.

2005 Stanford University School of Medicine, Tumor Biology Training Program, Stanford, CA.

2005 The Early Detection Symposium, Canary Fund, Stanford University, Stanford, CA.

2005 National Cancer Institute, Integrative Cancer Biology Program Mini-Symposia Berkeley, CA.

2005 University of California in San Francisco, 7th Annual Osher Lifelong Learning Institute and Mini Medical School, "Cancer Biology 101: Clues About New Treatments and Early Detection", UCSF.

2006 Amgen San Francisco, Seminar: "Therapeutic Approaches to Ras", South San Francisco, CA.

2006 Theravance Cancer Symposium, South San Francisco, CA.

2006 Lick-Wilmerding High School, Honors Biology: Genetics and Evolution Class, San Francisco, CA.

2006 UCSF Mini Medical School for the public course "Cancer: Bench to Bedside", UCSF.

2007 Novartis Seminar: "Drug targets in the Ras pathway," Emeryville, CA.

2007 UCSF Biomedical Sciences Graduate Program Session: "Cancer Biology and Cell Signaling and Tissue/Organ Biology & Edocrinology", UCSF.

2007 UCSF Department of Pathology: "Molecular Pathology and Biology of Neoplasia Course", UCSF.

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| 2007 | American Association for Cancer Research Translational Cancer Medicine Think Tank, Sonoma, CA. |
| 2007 | Stanford Cancer Center and Stanford University School of Medicine, Comprehensive Cancer Research Training Program Keynote Address, Stanford, CA. |
| 2007 | Stanford Medical School Cancer Biology Retreat Keynote Speaker, Palo Alto, CA. |
| 2008 | Lick-Wilmerding High School, Honors Biology: Genetics and Evolution Class, San Francisco, CA. |
| 2008 | UCSF Cancer Club, Therapeutics Challenges of Melanoma, UCSF. |
| 2008 | UCSF Herbert W. Boyer Program in Biological Sciences (PIBS), 1st Year Students Lecture: "Ras signaling in normal cells and cancer," San Francisco, CA. |
| 2008 | UCSF Helen Diller Family Comprehensive Cancer Center 2008 Symposium: Stem Cells and Cancer, San Francisco, CA. |
| 2009 | UCSF Emeriti Faculty Association: "Targeting the Ras Pathway.", San Francisco, CA. |
| 2009 | UCSF 3rd International Symposium on Cancer Metastasis and the Lymphovascular System: Basis for Rational Therapy: "Cancer Therapy based on Oncogene Action", San Francisco, CA. |
| 2009 | Molecular Therapeutics of Cancer Research Conference 2009: Session Leader "Oncogene Addiction", Stanford, CA. |
| 2009 | Genetic Syndromes of the Ras/MAPK Pathway: From Bedside to Bench and Back, Keynote Speaker: "New Perspectives on an Ancient Pathway", Berkeley, CA |
| 2009 | UCSF Workshop on Nutrition, Translational Medicine and Prostate Cancer, San Francisco, CA |
| 2009 | UCSF Helen Diller Family Comprehensive Cancer Center 2009 Symposium: The Prevention of Cancer, San Francisco, CA |
| 2009 | Population Sciences Special Interest Group (PopSci SIG) Face-to-Face Meeting hosted by HDFCCC and the NCI, San Francisco, CA |
| 2010 | UCSF Pancreas Cancer Program Retreat, San Francisco, CA |
| 2010 | AACR Think Tank on Clinical and Translational Cancer Research, San Francisco, CA |
| 2010 | 2010 UCSF Breast Oncology Program Scientific Retreat, San Francisco, CA |
| 2010 | Society for Basic Urologic Research / Society of Urologic Oncology Spring Meeting, San Francisco, CA |
| 2010 | UCSF Prostate Cancer Program Retreat, San Francisco, CA |
| 2010 | Novartis Institute for Biomedical Research Seminar, Emeryville, CA |

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| 2010 | UCSF Clinical and Translational Science Planning Meeting, San Francisco, CA |
| 2010 | Stanford Cancer Center and Stanford University School of Medicine, Comprehensive Cancer Research Training Program Plenary Lecture, Stanford, CA |
| 2010 | UCSF Cancer, Immunity & Microenvironment Symposium, San Francisco, CA |
| 2010 | UCSF Biomedical Sciences Retreat, Lake Tahoe, CA |
| 2010 | USF Cancer Research Translational Medicine Seminar, San Francisco, CA |
| 2010 | UCSF Helen Diller Family Comprehensive Cancer Center Symposium on Biology and Treatment of Brain Cancers, San Francisco, CA |
| 2011 | UCSF Breast Oncology Program Scientific Retreat, San Francisco, CA |

**CME COURSES ATTENDED:** Not Applicable

**GOVERNMENT and OTHER PROFESSIONAL SERVICE:**

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|---|---|
| 1996 | National Cancer Institute Working Group of Preclinical Models for Cancer |
| 1997-now | National Cancer Center Directors Working Group |
| 1998-1999 | National Cancer Institute Developmental Therapeutics Program Scientific Advisory Board |
| 1998-2003 | National Cancer Institute Board of Scientific Counselors Advisory Committee |
| 2003-now | National Cancer Institute Initiative for Chemical Genetics External Scientific Committee |
| 2004-now | National Cancer Institute Integrative Biology Program |

**UNIVERSITY AND PUBLIC SERVICE:**

**UNIVERSITY SERVICE:**

**SYSTEMWIDE:**

| | | |
|---|---|---|
| 2002-2003 | University of California, Irvine-Cancer Center | External Advisory Board |
| 2001-now | University of California Cancer Centers Consortium | Member |

**UCSF CAMPUS-WIDE:**

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| 1998-now | Mount Zion Subcommittee, Chancellor's Advisory Committee on the 2002 LRDP Amendment Sokolow Memorial Cancer Endowment Lectureship Committee, Chair |
| 2002-2003 | Parnassus Heights Leadership Council |
| 2002-now | Academic Planning Subcommittee, Chancellor's Advisory Committee on the Long Range Development Plan Amendment (Hospital Replacement) |
| 2006-now | UCSF's Strategic Planning Initiative Board Member and Subcommittee Member: Strategy Design Team B-Research Directions |

**SCHOOL OF MEDICINE:**

| | | |
|---|---|---|
| 1998 | LCME Subcommittee on Research, and Graduate Education in Basic Sciences | |
| 1998-now | Biomedical Sciences Program (BMS) | Member |
| 1998-now | Herbert Boyer Program in Biological Sciences (PIBS) | Member |
| 1999-2001 | Preuss Molecular Neuro-Oncology Search Committee | Member |
| 2000-2003 | Developmental Research and Fellowship Committee | Member |

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| | (Department of Urology) | |
| 2000-now | Executive Committee Prostate Cancer SPORE (Department of Urology) | Member |
| 2000-now | Advisory Review Committee Prostate Cancer SPORE (Department of Urology) | Member |
| 2000-now | Prostate Cancer Career Development Program (Department of Urology) | Ad Hoc Member |
| 2002 | School of Medicine, Hematology Oncology Faculty Search Committee | Member |
| 2002-2003 | Academic Planning Subcommittee of the Chancellor's Advisory Committee on the LRDP Amendment | Member |
| 2002 | School of Medicine, Microbiology Faculty Search Committee | Member |
| 2002-2003 | School of Medicine, Dean's Search Committee | Member |
| 2003-now | School of Medicine Medical Scientist Training Program | Faculty Advisor |
| 2003-now | Brain Tumor Research Center, Department of Neurological Surgery | Associate Member |
| 2004 | School of Medicine, Chair of the Department of Obstetrics, Gynecology and Reproductive Sciences Search Committee | Member |
| 2005-2007 | CTSA Senior Leadership Group Committee | Member |
| 2005-2007 | School of Medicine, Department of Obstetrics, Gynecology and Reproductive Sciences Director, Division of Gynecologic Oncology | Member |
| 2006-now | Pharmacogenetics of Membrane Transporters Scientific Advisory Board | Member |
| 2006-2006 | School of Medicine, CTSI Principal Investigator Search Committee (Department of Medicine) | Member |
| 2006-2007 | School of Medicine, CTSI Executive Director Search Committee (Department of Medicine) | Member |
| 2006-2007 | School of Medicine, Radiation Oncology Search Committee (Department of Medicine) | Member |
| 2006-2007 | School of Medicine, Chair, Department of Medicine Search Committee | |
| 2007-now | School of Medicine, Hematology and Oncology Division Chief Search Committee (Department of Medicine) | Member |
| 2008-now | School of Medicine, Dean's Search Committee | Member |
| 2008-now | Pancreas SPORE Internal Advisory Board (Department of Medicine, Division of Hematology and Oncology) | Member |
| 2009 | Department of Medicine, OB/Gyn & RS Search Committee for Assistant/Associate Professor in Residence, Division of Gynecologic Oncology | Member |
| 2009 | Department of Medicine, Division of Hematology and Oncology, Search Committee for Assistant/Associate Professor in-Residence, Urologic Oncology | Member |
| 2009 | Office of the Vice Chancellor Search Committee, Executive Director of Research Resource Program | Member |
| 2010 | School of Medicine, Hematology and Oncology Professor In-Residence Search Committee | Member |
| 2011 | School of Medicine, Department of Urology Urologic Oncology Faculty Search Committee | Member |
| 2011 | Waxman Foundation Award Selection Committee | Member |

**DEPARTMENTAL SERVICE:**
**Helen Diller Family Comprehensive Cancer Center:**

| | | |
|---|---|---|
| 1997-1999 | Laboratory Sciences Steering Committee | Member |
| 1997-now | American Cancer Society Institutional Research Grant Program Award Review Committee | Member |
| 1998-now | Mount Zion Health Fund Institutional Research Award Review Committee | Member |
| 1998-now | Directors Group | Chair |
| 1998-now | Executive Committee | Chair |
| 1998-now | Program Leaders Committee | Chair |
| 1998-now | Prostate Cancer Program Steering Committee | Chair |
| 1998-now | Scientific Advisory Council, Lab Sciences Committee | Chair |
| 1999-now | Breast Oncology Program | Program Member |
| 1999-now | Cell Cycling and Signaling | Program Member |
| 1999-now | Maurice, Ethel, and Jane Sokolow Memorial Cancer Endowment Committee | Chair |
| 1999-now | Alexander and Margaret Stewart Trust Endowment Committee | Chair |
| 2000-now | Cancer Research Building Space Review Committee | Chair |
| 2003-2008 | Clinical Cancer Center Governing Board | Chair |
| 2000-2001 | Search Committee for Associate Director of Education and Outreach | Chair |
| 2000-2001 | Search Committee for Associate Director of Epidemiology Prevention and Control | Chair |
| 2001-now | Critical Players at Mount Zion Committee | Member |
| 2005-now | UCSF Helen Diller Family Comprehensive Cancer Center Community Advisory Board | Member |
| 2007 | Cancer Center Naming Event Ad Hoc Committee | Member |
| 2008 | Diller Governance Building Committee | Member |

**PUBLIC SERVICE:**

Fundraising

2006 - $150 Million Pledge for the UCSF Helen Diller Family Comprehensive Cancer Center. Participated in 22 months of negotiations resulting in a gift of $150M. Met with the donors and UCSF leadership to define the vision and craft a proposal that aligned the needs of the Center with the interests of the donor to secure the gift.

On average, participated in approximately 30 donor solicitation visits annually. Since 2003, solicitations were done in support of the Mission Bay Campaign, the Cancer Research Building Campaign, Atwater Projects for Breast Cancer, and the ongoing solicitation of gifts for the programs, faculty, and general support of the Center.

Participated in quarterly planning meetings to review strategy for direct mail and programmatic fundraising efforts to benefit the Cancer Center general fund. In the first year, this program produced net revenue of approximately $70,000 and, in year five years, it is producing approximately $450,000 net revenue. The program now includes an option for donors to direct gifts to programmatic areas of the Center and the costs are underwritten by the Helen Diller Family Comprehensive Cancer Center.

Monthly meetings with the development staff. Fundraising for Cancer at UCSF has risen from $28 million in FY03 to $61 million in FY07.

Donor Stewardship and Institutional Service

On average, participated in 24 donor stewardship activities annually to maintain relationships with principal and major donors to the Helen Diller Family Comprehensive Cancer Center. One such donor is now a major donor ($25M) to the new hospital campaign.

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| Since 1996 | Participated in the biennial "Raising Hope" benefit for the UCSF Helen Diller Family Comprehensive Cancer Center. Attended, presented, and purchased a table at each of six Raising Hope events held to date. In 2007, the sixth event raised over $3.75M. Since inception the event has raised awareness and over $21M for the Cancer Center. |
| Since 1999 | Presenter at the annual UCSF Helen Diller Family Comprehensive Cancer Center Symposium |
| Since 2003 | Presented at Cancer Council meetings and met with several Cancer Council members each year |
| May 2004 | Spoke at the opening of the AVON Foundation Comprehensive Breast Center, a state-of-the-art woman's imaging center at San Francisco General Hospital |
| Since 2005 | Speaker at the Annual Canary Foundation National EDI Stakeholders Symposium and participate in the Annual Canary Foundation's Gala Event "Cabana". In 2006, participated in The Canary Foundation CXO and Celebrity Go-Kart Challenge and recruited a race car driver to participate in the event and sponsor a $10,000 table for the 2006 Cabana gala event. |
| Feb 2006 | Salute to Excellence Awards Gala, American Liver Foundation. Personally sponsored a $5,000 table on behalf of the UCSF Comprehensive Cancer Center. |
| May 2007 | Attended Welcome Reception of the National Association of Cancer Center Development Officers and Public Affairs and Marketing Network Conference |
| July 2007 | Attended UCSF Advancement Resources Development Workshop |
| Nov 2007 | Speaker at the naming event for the Helen Diller Family Comprehensive Cancer Center |
| Nov 2007 | Speaker in a DVD presented at the Foundation Annual Meeting |
| Feb 2008 | Speaker at the Mount Zion Auxiliary Board of Directors Meeting |
| Feb 2008 | Attended the Paving the Way 2008 event in benefit of the Larkin Street Youth Services |
| Mar 2008 | Participated in the 2-day Atlantic Philanthropies Symposium |
| Apr 2008 | Presented and co-hosted a table at the Chancellor's Dinner held at SFMOMA |

Foundation Advisory Boards:

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| 2004-now | Canary Foundation Scientific Advisory Board |

2006-now Melanoma Research Foundation Board Member and Scientific Advisory Board

## TEACHING and MENTORING:

### FORMAL SCHEDULED CLASSES FOR UCSF STUDENTS:

| Qtr | Academic Yr | Course No & Title | Teaching Contribution | Class size |
|---|---|---|---|---|
| Winter | 2004 | Biochem 297: Molecular Pathology and Biology of Neoplasia | Lecture | 25 |
| Fall | 2006 | Cancer Block IDS 106: Cancer: Bench to Bedside (CBB) | Lecture: Frontiers in Cancer Therapy | 35 |
| Winter | 2007 | Biochem 297: Molecular Pathology and Biology of Neoplasia | Lecture: New Approaches to Cancer Treatment & Rational Therapy | 25 |
| Winter | 2007 | UCSF Herbert W. Boyer Program in Biological Sciences (PIBS), 1st Year Students Lecture | Lecture: Ras signaling in normal cells and cancer | 25 |

### POSTGRADUATE AND OTHER COURSES:

| Qtr | Academic Yr | Course No & Title | Teaching Contribution | Class size |
|---|---|---|---|---|
| Winter | 2004 | MSU04004: 3rd Annual UCSF Clinical Cancer Update, Department of Surgery | Lecture: Cancer Therapy Based on Oncogenes and Tumor Suppressors | 50-75 |
| Summer | 2005 | Elective: UCSF Mini Medical School for the Public | Lecture: New Horizons on the War on Cancer: Theory to Therapy | 75-100 |
| Fall | 2005 | MLL06001: UCSF Mini Medical School for the Public, Cancer Biology 101: Clues About New Treatments and Early Detection | Lecture: New Treatments and Early Detection | 75-100 |
| Summer | 2007 | MMC08003: 1st International Costello Syndrome Research Symposium 2007 | Session Moderator: Treatment Modalities Lecture: Overview to Treatment Options | 150-200 |

### STUDENTS SUPERVISED OR MENTORED:

| Dates | Name | Fellow | Faculty Role | Current Position |
|---|---|---|---|---|
| Spring 2009 | Phillip Greyling | Spring Intern | Advisor | Student – UC Santa Cruz |
| 2009 | Vritti Goel | Summer Intern | Advisor | Student – Scripps College, Claremont, CA |
| 2009 | Alison Altman | Summer Intern | Advisor | Student – Yale College, New Haven, CT |

### PREDOCTORAL STUDENTS SUPERVISED OR MENTORED:

| Dates | Name | Fellow | Faculty Role | Current Position |
|---|---|---|---|---|
| 1997 | Eric Collisson, MD | Summer Intern | Advisor | Senior Fellow, Div. of Hematology/Oncology, UCSF |
| 1999-2000 | Kenichi Wakita | Daiichi-Sankyo, Ltd | Masters, 1989, Tokyo Institute of Technology | Staff Scientist, Daiichi-Sankyo, Ltd. |
| Spring 2001 | Michelle Shih | UCSF Biomedical Sciences Program | Rotation Advisor | 2007 Graduate |
| Spring 2001, Fall 2001-Summer 2006 | Demetris Iacovides | UCSF Biomedical Sciences Program | Thesis Advisor (joined lab Fall 2001) | Post-doctoral Fellow, Lawrence Berkeley National Laboratory, Gray Lab |
| Fall 2001 | Curtis Pickering | UCSF PIBS Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Summer 2002 | Felicia Yen | High School Summer Intern | Supervisor | Undergraduate, Harvard University |
| Fall 2002 | Jaime Lopez | UCSF-SFSU PREP | Rotation Advisor | UCSF Cancer Research |

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|---|---|---|---|---|
| | | Program | | Institute, Toczyski Lab |
| Winter 2002 | Erika Woodbury | UCSF PIBS Program | Rotation Advisor | Postdoctoral Scholar, McCormick Lab, UCSF |
| Winter 2002 | Yong Ping Crawford | UCSF Biomedical Sciences Program | Rotation Advisor | Unknown |
| Winter 2003, Summer 2003-present | Abigail Miller | UCSF Biomedical Sciences Graduate Program | Thesis Advisor (joined lab Summer 2003) | UCSF Cancer Research Institute, McCormick Lab |
| Spring 2003, Summer 2003-present | Cynthia Mysinger | UCSF Biomedical Sciences Program | Thesis Advisor (joined lab Summer 2003) | Pre-doctoral Scholar, UCSF |
| Fall 2003 | Cory Nicholas | UCSF Biomedical Sciences Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Fall 2003 | Mina Nikanjam | UCB - Bioengineering | Rotation Advisor | Unknown |
| Fall 2003-Winter 2008 | Vernon Phan | UCSF Biomedical Sciences Program | Thesis Advisor (joined lab Winter 2003) | Post-doctoral Fellow, Genentech, Inc. |
| Winter 2004 | Vanessa Angeles | UCSF Biomedical Sciences Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Spring 2004, Summer 2004-present | Jesse Lyons | UCSF Biomedical Sciences Program | Thesis Advisor (joined lab Summer 2004) | UCSF Cancer Research Institute, McCormick Lab |
| Summer 2004, Fall 2005-Spring 2007 | Ammanuel Asmamaw | UCLA Graduate/UCSF-SFSU PREP Program | Rotation Advisor | Research Associate, Department of Surgery, Stanford University |
| Fall 2004 | Michael D'amborasia | UCSF PIBS Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Fall 2004-present | Amy Young | UCSF Biomedical Sciences Program | Thesis Advisor | UCSF Cancer Research Institute, McCormick Lab |
| 2005-2007 | Jennifer Okada | UCLA Graduate/CRI Junior Specialist | Supervisor | Research Associate, Exelixis, Inc. |
| 2005-2007 | Mayumi Kitagawa | Daiichi-Sankyo, Ltd/CRI Assistant Specialist | Supervisor | Staff Scientist, Daiichi-Sankyo, Ltd. |
| Fall 2005 | Alana Lerner | UCSF Biomedical Sciences Graduate Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Fall 2005 | Nichole Reyes | UCSF Biomedical Sciences Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Fall 2005 | Noel Moreno | UCSF-SFSU PREP Program | Rotation Advisor | San Francisco State University Graduate Student |
| Fall 2005, Fall 2006-present | Michael Nehil | UCSF TETRAD Program | Thesis Advisor (joined lab Winter 2006) | UCSF Cancer Research Institute, McCormick Lab |
| Summer 2006 | Frank Bos | University Medical Center, Utrecht | Internship Rotation Advisor | Pre-doctoral Scholar, Utrecht, The Netherlands |
| Summer 2006, Fall 2006-present | Irma Rangel | UCSF TETRAD Program | Thesis Advisor (joined lab Winter 2006) | UCSF Cancer Research Institute, McCormick Lab |
| Fall 2006 | Jeffrey Alexander | UCSF Biomedical Sciences Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Fall 2006 | Renee Vanderlaan | UCSF Biomedical Sciences Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Summer 2006-present | Daniel Garcia | UCSF Biomedical Sciences Program | Thesis Advisor | Pre-doctoral Scholar, UCSF |
| Fall 2007 | Angela Rojas | UCSF Biomedical Sciences Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Fall 2009-present | Kegan Warner | UCSF Biomedical Sciences Program | Thesis Advisor | Pre-doctoral Scholar, UCSF |
| Fall 2009-present | Danielle Shin | UCSF Biomedical Sciences Program | Thesis Advisor | Pre-doctoral Scholar, UCSF |
| Winter 2010 | Joseph Juan | UCSF TETRAD Program | Rotation Advisor | Pre-doctoral Scholar, UCSF |
| Winter 2010 | Lawrence Lin | UCSF - Pharmaceutical Sciences and | Rotation Advisor | Pre-doctoral Scholar, UCSF |

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| | | Pharmacogenomicsm | | |

**POSTDOCTORAL FELLOWS AND RESIDENTS DIRECTLY SUPERVISED:**

| Dates | Name | Prior Academic Degree | Title of Research Project | Faculty Role | Current Position |
|---|---|---|---|---|---|
| 1975-present | Madhu Macrae | Ph.D., 1997 UCSF Microbiology | A Potential New Approach to Targeted Cancer Therapy | Research Advisor | Specialist, UCSF Cancer Research Institute |
| 1996-2000 | Rui-hong Chen | Ph.D., 1994, SUNY Stony Brook, NY | Regulation of β-catenin and colon cancer therapeutics | Research Advisor | Staff Scientist, Nexgenix Pharmaceuticals, LLC |
| 1997-1999 | Osamu Tetsu | M.D., 1989, Ph.D., 1997, Chiba University, Japan | β-catenin regulated cyclin D1 expression in colon carcinoma cells | Research Advisor | Assistant Adjunct Professor, Department of Otolaryngology, Head & Neck Surgery, UCSF |
| 1997-2000 | Jingwu Xie | Ph.D., 1994, Dundee University | The hedgehog signaling pathway and human cancer | Research Advisor | Associate Professor, University of Texas Medical Branch |
| 1997-2001 | Peter Sabbatini | Ph.D., 1997, Rutgers University, NJ | PKB & p53 dependent apoptosis | Research Advisor | Staff Scientist, Celera Corporation |
| 1997-2002 | Wei Vivianne Ding | Ph.D., 1997, University of Texas, Southwestern Medical Center | Regulation of GSK3 in cancer cells and Wnt signaling pathway | Research Advisor | Assistant Researcher, UCSF Department of Surgery |
| 1997-2007 | Pablo Rodriguez-Viciana | Ph.D., 1997, University College, London | Role of PI 3 Kinase in Ras induced tumor genesis | Research Advisor | Associate Professor, University College of London, UK |
| 1997-1998 | Michael Korn | M.D., 1988, University of Dusseldorf | Adenovirus tumor cell interaction | Research Advisor | Associate Professor of Medicine, Department of Gastroenterology, UCSF |
| 1997-2000 | Katherine A. Rauen | Ph.D., 1992, MD, 1995, UC Davis | Mouse model for E1b55k deleted mouse adenovirus | Research Advisor | Adjunct Professor, Department of Pediatrics, UCSF |
| 1997-2001 | Haiyan Jiang | Ph.D., 1997, University of Wisconsin Madison | Mechanism of parvovirus induced the cell killing in human transformed cells | Research Advisor | Staff Scientist, Amgen Corporation |
| 1998-2001 | Stefan Ries | Ph.D., 1998, University of Regensburg, Bavaria | Mechanisms of 015 replication in colon cancer cell lines | Research Advisor | Staff Scientist, MediGene, Munich, Germany |
| 1998-2006 | Clodagh O'Shea | Ph.D., 1997, Imperial College of Science & Technology, University of London | The role of PML in viral replication and oncogenesis and adenoviral replication in primary cells | Research Advisor | Assistant Professor, UCSD, The Salk Institute |
| 1998-1999 | Christopher Haqq | M.D., 1996, Ph.D., 1996, Harvard Medical School | Prostate Cancer Gene Expression | Research Advisor | Assistant Adjunct Professor, Department of |

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|---|---|---|---|---|---|
| | | | | | Urology, UCSF/Sr. Director of Clinical & Research Development, Cougar Biotech, Inc. |
| 1998-1999 | Tomoko Tominaga | M.D., 1984, Ehime Univ.Faculty of Medicine, Ph.D. 1993 Kyoto Univ. Faculty of Medicine | Studies of diaphanous related formins as Rho effector proteins | Research Advisor | Professor, Dept of Bio-Enviromental Science, Cell Signaling, National Institute for Physiological Sciences, Aichi, Japan |
| 1999-2001 | Carola Biederer | Ph.D., 1999, University of Aachen | Role of Ras induced MDM2 in tumor genesis | Research Advisor | Staff Scientist, Roche, Munich, Germany |
| 1999-2007 | Luika Timmerman | Ph.D., 1998, Stanford University | Wnt signaling in the mammary gland | Research Advisor | Assistant Research Molecular Biologist, UCSF Cancer Research Institute |
| 2000-2003 | Masashi Aonuma | Ph.D., 1999, Tokyo University | Analysis of ARF expression | Research Advisor | Manager, Biological Research Laboratories , R&D Division, Daiichi-Sankyo, Ltd. |
| 2001-2003 | Jay Gump | Ph.D., 2001 Univ. of Vermont | Post-translational regulation in the CDK4 pathway | Research Advisor | Consultant, Unknown Company Profile |
| 2001-2004 | Jennifer Yeh | Ph.D., 2001, University of Texas | Microarray analysis of gene expression in breast cancer | Research Advisor | Consultant, Unknown Company Profile |
| 2002-present | Sang-Hyun Lee | Ph.D., 2002, Univ. of MO-Columbia | P53 ARF pathway Analysis | Research Advisor | National Research Foundation Fellow/Singapore |
| 2002-2005 | Hiroshi Okabe | Ph.D., 2001, Kyoto University, Japan | Mechanisms of cyclin D1 proteolysis | Research Advisor | Laboratory Medicine, Human Genome Center, University of Tokyo, Japan |
| 2004-2005 | Jimbo Takeshi | Ph.D., 2002, University of Tokyo | Cancer research focusing on preclinical and clinical biomarkers for potent MDM2 inhibitors | Research Advisor | Staff Scientist, Daiichi-Sankyo Ltd., Japan |
| 2004-2008 | Anthony Karnezis | M.D., Ph.D., 1996, 2002, Northwestern University/ Albert Einstein College of Medicine | Lung Cancer: Small cell and non-small cell | Research Advisor | Postdoctoral Scholar, UCSF Cancer Research Institute |
| 2004-2006 | Seiko Ishida | Ph.D., 2001, UCSF | Studying the mechanism by which cells become addicted to Ras through suppression of apoptosis | Research Advisor | Assistant Research Biochemist, UCSF Cancer Research Institute |
| 2005-2007 | Katsutoshi Oda | M.D., Ph.D., 1994, 2001, University of Tokyo | Cancer research focusing on preclinical and clinical biomarkers for potent MDM2 inhibitors | Research Advisor | Associate Professor, Department of Obstetrics & Gynecology, University of Tokyo, Japan |

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|---|---|---|---|---|---|
| 2007-2010 | Erika Woodbury | Ph.D. 2007, UCSF PIBS Program | Investigation of the role of the tumor suppressor protein neurofibromin in the DNA damage response | Research Advisor | Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center |
| 2007-2008 | Heather Christofk | Ph.D., 2007, Harvard Medical School | Metabolic Changes in Cancer Cells | Research Advisor | Asst. Professor, Inst. for Molecular Med. (IMED), UCLA |
| 2007-present | Takahiko Seki | Ph.D., 2002, University of Tokyo | Involvement of MdmX in Nutlin-sensitivity | Research Advisor | Associate Specialist, UCSF Cancer Research Institute/Daiichi-Sankyo, Ltd. |
| 2008-present | Matthew Holderfield | Ph.D., 2007, UC Irvine | Signaling pathways downstream of Ras | Academic Mentor | Postdoctoral Scholar, Novartis Institutes for Biomedical Research |
| Spring 2003, Summer 2003-2010 | Cynthia Mysinger | Ph.D. 2009, UCSF Biomedical Sciences Program | Thesis Advisor (joined lab Summer 2003) | Research Advisor | Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center |
| 2008-present | Tanja Tamguney | PhD | Self-amplifying plasmids for cancer therapy | Research Advisor | Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center |
| 2010-present | Tina L. Yuan | PhD | | Research Advisor | Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center |
| 2010-present | Ellen O'Dea | PhD | | Research Advisor | Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center |

**INFORMAL TEACHING:**

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|---|---|
| 1999-now | Bimonthly research advisor/mentor meetings with graduate students and postdoctoral scholars/fellows |
| 1999-now | Weekly laboratory meetings (graduate students and postdoctoral scholars/fellows) |
| 2006 | Lick-Wilmerding High School, Honors Biology: Genetics and Evolution Class, San Francisco, CA. |
| 2008 | Lick-Wilmerding High School, Honors Biology: Genetics and Evolution Class, San Francisco, CA. |
| 2008-now | Quarterly meetings with Post-doctoral Scholar from the Novartis Institutes for Biomedical Research Postdoctoral Program |

**FACULTY MENTORING**

**FACULTY MENTORED:**

| Dates | Name | Position while Mentored | Mentoring Role | Current Position |
|---|---|---|---|---|
| 2007-now | John K. Chan, MD | Assistant Professor | Assigned Faculty Mentor/Advisor | Assist Prof, OB, GYN & Reproductive Sci, UCSF |
| 1997-now | W. Michael Korn, MD | Postdoc and now Associate Professor | Research Advisor/Co-Investigator on U54 grant | Associate Prof, Div of GI & Med Onc, UCSF |
| 1997-now | Osamu Tetsu, MD, PhD | Postdoc and now Assistant Adjunct Professor | Academic and Research Advisor | Assist Adjunct Prof, Dept of Otolaryngology, Head & Neck Surgery, UCSF |
| 1999-now | David Jablons, PhD | Assistant Professor of Surgery | Research Advisor/Scientific Collaborator | Ada Distinguished Prof of Thoracic Onc, Dept of Surgery, UCSF |
| 1997-now | Katherine A. Rauen, MD, PhD | Postdoc and now Adjunct Professor | Research Advisor/Co-sponsor on K23 Grant | Assistant Adjunct Professor, Dept of Pediatrics, Div of Medical Genetics, UCSF |

**OTHER VISITING FACULTY SUPERVISED:**

| Dates | Name | Position while Mentored | Mentoring Role | Current Position |
|---|---|---|---|---|
| 1998-1999 | Pierre Chardin, PhD | Visiting Scholar | Research Advisor | Researcher, Institut de Pharmacologie du CNRS, France |
| 1999-2000 | Michael Fried, PhD | Visiting Scholar-Sabbatical | Research Advisor | Adjunct Professor, UCSF Cancer Research Institute |
| 2002 | Alexander Levitzki, PhD | Visiting Scholar-Sabbatical | Research Advisor | Professor, The Institute of Life Sciences, The Hebrew University of Jerusalem |
| 2005 | Giannoulis Fakis, PhD | Visiting Scholar-Sabbatical | Research Advisor | Lecturer, Democritus University of Thrace, Dept of Molecular Biology and Genetics, Greece |
| 2006 | Giannoulis Fakis, PhD | Visiting Scholar-Sabbatical | Research Advisor | Lecturer, Democritus University of Thrace, Dept of Molecular Biology and Genetics, Greece |
| 2008-2009 | Laura van 't Veer, PhD | Visiting Scholar-Sabbatical | Research Advisor | Professor, The Netherlands Cancer Institute |

**TEACHING AIDS:**

UCSF: 2006 Cancer Block IDS 106: Cancer: Bench to Bedside (CBB), Frontiers in Cancer Therapy Lecture Syllabus for 2nd year medical students and exam questions.

**OTHER:**
**See visiting Professorships and service lectures listed under "Invited Presentations"**

**TEACHING AWARDS AND NOMINATIONS:**
**See Honors and Awards**

**SUMMARY OF TEACHING HOURS: (including preparation)**

2007-now 563 total hours of teaching and mentoring
Formal Class or course teaching hours: 23 hours
Informal teaching hours: 180 hours
Mentoring hours: 360 hours

2008-2009: Total anticipated hours of teaching and mentoring: 563 hours (as above)

**TEACHING NARRATIVE:**

My recent teaching activities have been dedicated to two roles: research advisor and mentor to faculty, graduate students, and postdoctoral scholars. I have taught and supervised 32 pre-doctoral students, 31 postdoctoral scholars/fellows, 5 faculty members, and 5 visiting scholars. I have taught scientific concepts and techniques during weekly meetings with my laboratory members and closely supervised the work of postdoctoral researchers in my lab at the UCSF Helen Diller Family Comprehensive Cancer Center. Three postdocs from my lab have stayed at UCSF (Drs. Korn, Rauen, and Tetsu) and I continue to mentor them, assist them with grants and papers, and collaborate where appropriate. Recently, Dr. Rauen published in *Science*, assisting her at several levels. Dr. Tetsu has published highly cited papers in *Nature* and *Cancer Cell*. Dr. Korn has published in *PNAS* and *Nature Medicine*. Recently, I have cut down the number of institutions and companies that I consult for to spend more time with my students and postdocs, as well as mentoring junior faculty. I participate in Cancer Club, PIBS, BMS, etc., and serve as faculty advisor to the MSTP program.

**RESEARCH AND CREATIVE ACTIVITIES**

**RESEARCH AWARDS AND GRANTS:**

**CURRENT**

P30 CA82103 McCormick (PI) 09/25/2007-05/31/2012
NIH/NCI $3,624,403 direct/yr 1
Cancer Center Support Grant $19,550,266 Total direct/yrs 1-5
The Cancer Center Support Grant provides support for administration and infrastructure for the UCSF Comprehensive Cancer Center. Dr. Frank McCormick is the Director of the Cancer Center.

Daiichi-Sankyo Pharmaceuticals Contract (PI) 8/06/2004 – 2/1/2011
Preclinical Evaluation of Drugs that Inhibit Mdm2 $594,060 direct/yr 1
The major goal of this project is to develop inhibitors of Mdm2 as cancer therapeutics. $1,274,250 Total direct/yrs 1-3

American Assn for Cancer Research (PI) 7/1/2010-6/30/2012
Specific K-Ras Inhibitors for treating pancreatic cancer $180,000 direct/yr 1-2
The major goals of this project are to propose a new effort to target the C-terminus of K-Ras 4B, the major form of K-Ras expressed in pancreatic cancer cells, by identifying small molecules that bind to this region and covalently modify cysteine-186 to prevent lipid modification and block K-Ras 4B function in cancer cells.

U54CA143836 (Liphardt)(Co-Investigator) 9/29/2009-7/31/2014
UC Berkeley $80,239 direct/yr 1
Fundamental Mechanobiology of Tumor Progression $423,527 Total direct/yrs 1-5
The major goals of this project are to evaluate potential therapeutic applications of the projects and addressing questions that of highest clinical impact

**PENDING**

Lustgarten Foundation (PI) 11/1/2010 - 10/31/2013
$166,666 direct/yr 1
$661,146 Total direct/yrs 1-3
The major goal of this project is to develop and utilize human antibody-targeted nanoparticles to deliver small interfering RNAs to pancreatic tumor cells to inhibit K-ras function.

**PAST**

BIO07-10642-IND (PI) 2/1/2008 - 1/31/2011
Halozyme Therapeutics, Inc. $97,220 direct/yr 1
Self-Amplifying Plasmids That Kill Cancer Cells $194,307 Total direct/yrs 1-2
The major goal of this project is to study a combination of tumor selective amplification and gene expression to facilitate efficient and specific killing of tumor cells.

P50 CA 112970 (Korn) (Co-Investigator) 1/1/2005 – 12/31/2010
NIH/NCI $268,853 direct/yr 1
UC/Lawrence Berkeley Lab Subcontract $1,461,856Total direct/yrs 1-5
The major goal of this program is to develop and experimentally validate a computational model of Raf-MEK-ERK signaling in breast cancer that will predict individual responses to therapeutic agents that inhibit Raf-MEK-ERK signaling.

BIO07-10642-UC (PI) 2/1/2008 - 1/31/2010
UC Discovery-Biotechnology $118,633 direct/yr 1
Self-Amplifying Plasmids That Kill Cancer Cells $243,576 Total direct/yrs 1-2
The major goal of this project is to study a combination of tumor selective amplification and gene expression to facilitate efficient and specific killing of tumor cells.

P50 CA58207 Gray (Co-Investigator) 08/1/2002 - 11/30/2007
NIH/NCI $694,138 direct/yr 8
Bay Area Breast Cancer Translational Research Program $8,000,050 Total direct/yrs 8-13
Project 2
Therapeutic Implications of Amplification of Receptor Tyrosine Kinase (RTK) Signaling Pathway Genes
In this program, we will attempt to understand the molecular basis of the variable response amongst breast cancer cells to targeted therapeutics, such as Herceptin and EGF-receptor inhibitors.

P30 CA82103 (PI) 08/05/1999 – 08/31/2007
NIH/NCI $852,117direct/yr 1
Cancer Center Support Grant $29,343,177 direct/yrs 1-8
The Cancer Center Support Grant provides support for administration and infrastructure for the UCSF Comprehensive Cancer Center. Dr. Frank McCormick is the Director of the Cancer Center.

Onyx Corp. (PI) 01/28/2003 – 01/27/2007
Replicating Viruses for Treating Cancer $349,999.56 direct/yr 1
$1,082,698.01Total Total direct/yrs 1-3
The research project shall consist of experiments aimed at identifying/construction novel replicating viruses and methods/compositions of using the same for treating cancer.

Daiichi Pharmaceuticals (PI) 07/01/2001 - 06/30/2004
Survival Pathways in Cancer Cells $1,048,385 direct/yr 1
$3,089,786 Total direct/yrs 1-3
This program seeks to identify new targets for therapeutic intervention, based on signal transduction pathways that promote cancer cell survival. In collaboration with Daiichi, we will screen for drugs that block these pathways selectively.

Biostar02-10242 (PI) 01/28/2003-01/27/2006
UC Discovery Grant $349,999.56 direct/yr 1
Replicating Viruses for Treating Cancer $1,082,698.01Total direct/yrs 1-3
The goal of this project is to use molecular analysis of cancer cells infected with ONYX-015 to devise and test new strategies for improving efficacy of this promising new anti-cancer agent.

DAMD17-03-1-0170 (PI) 05/01/2003-05/31/2006
DOD Idea Award $148,152 direct/yr 1
Identification of Functions of Neurofibromin Distinct from RasGAP Domain $442,793Total direct/yrs 1-3
The goals of this project are to establish a system for blocking signals detected by neurofibromin and Ira proteins using yeast as a model organism; and to identify the nature of the signals using genetic, biochemical and genomic approaches.

Biostar02-10331 Gray (Co-Investigator) 08/19/2003-08/18/2006
UC Discovery Grant $100,000 direct/yr 1
Validating Breast Cancer Therapeutic Targets $300,000 Total direct/yrs 1-3
The overall goal of this project is to identify and validate new therapeutic targets in breast cancer and to identify candidate therapeutic agents against these targets.

Pilot Studies Award (PI) 10/01/2003-09/30/2004
National Neurofibromatosis Foundation $25,000 direct/yr 1
A Screen for IRA/Neurofibromin Functions Distinct from the GAP Domain $25,000 Total direct/yr 1
Major goals: Saccharomyces cerevisiae has two neurofibromin homologs, Ira1 and Ira2, whose functions can be complemented by the human protein, and whose homology with neurofibromin extends across most of the protein, including sequences flanking the GAP domain. We propose to study the functions of these flanking sequences using the power of yeast genetics and expression arrays.

## PEER REVIEWED PUBLICATIONS:


1. **McCormick, F.,** and Newton, A. A. 1975. Polyamine metabolism in cells infected with herpes simplex virus. *J Gen Virol* 27:25-33.
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## NON-PEER REVIEWED PUBLICATIONS AND OTHER CREATIVE ACTIVITIES:

### Books and Chapters:

### Book Chapters

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4. *The GTPase Superfamily,* Chairman: **McCormick F,** 1993.
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### PATENTS ISSUED OR PENDING (ALLOWED)

#### Issued Patents:

1. U.S. Patent No. **4,762,706** Peptide antibodies and their use in detecting oncogene products – 8/9/1988
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3. U.S. Patent No. **4,966,843** Expression of interferon genes in Chinese hamster ovary cells – 10/30/1990
4. U.S. Patent No. **5,057,410** Chimeric messenger RNA detection methods – 10/15/1991
5. U.S. Patent No. **5,104,975** Compositions for detecting ras gene proteins and cancer therapeutics – 4/14/1992
6. U.S. Patent No. **5,234,839** Compositions for detecting ras gene proteins and cancer therapeutics – 8/10/1993
7. U.S. Patent No. **5,376,567** Expression of interferon genes in Chinese hamster ovary cells – 12/27/1994
8. U.S. Patent No. **RE35,171** Compositions for detecting ras gene proteins and cancer therapeutics – 3/5/1996
9. U.S. Patent No. **5,610,276** Polypeptides and antibodies derived from GAP associated protein, p62 – 3/11/1997
10. U.S. Patent No. **5,635,399** Retroviral vectors expressing cytokines – 6/3/1997

11. U.S. Patent No. **5,652,130** Retroviral vectors expressing tumor necrosis factor (TNF) – 7/29/1997
12. U.S. Patent No. **5,677,178** Cytopathic viruses for therapy and prophylaxis of neoplasia - 10/14/1997
13. U.S. Patent No. **5,731,427** Nucleic acids encoding a gap-associated protein – 3/24/1998
14. U.S. Patent No. **5,760,203** Gap gene sequences – 6/2/1998
15. U.S. Patent No. **5,763,573** GTPase activating protein fragments – 6/9/1998
16. U.S. Patent No. **5,773,237** Method for determining tyrosine kinase activity – 6/30/1998
17. US. Patent No. **5,801,029** Cytopathic viruses for therapy and prophylaxis of neoplasia – 9/1/1998
18. U.S. Patent No. **5,846,945** Cytopathic viruses for therapy and prophylaxis of neoplasia – 12/8/1998
19. U.S. Patent No. **5,856,181** Cytopathic viruses for therapy and prophylaxis of neoplasia – 1/5/1999
20. U.S. Patent No. **5,972,706** Cytopathic viruses for therapy and prophylaxis of neoplasia – 10/26/1999
21. U.S. Patent No. **6,617,496** Effecting virus resistance in plants through the use of negative strand RNAs – 9/9/2003
22. U.S. Patent No. **6,787,321** Mammalian two-hybrid system for screening for modulators of the accumulation of metabolic products – 9/7/2004
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**OTHER CREATIVE ACTIVITIES:**

Melanoma Therapeutics Foundation Website Portal
http://melanomatherapeutics.org/index.html

UCSF/Halozyme Therapeutics, Inc. Sharepoint Collaboration Website
https://cc-sharepoint.ucsf.edu/mccormick/biostar/default.aspx

ProteinPlanet,Inc.
www.proteinplanet.com

**ABSTRACTS**

1991 **McCormick, F.** "The Success And Failure Of Targeted Therapies." International Melanoma Congress.
1997 **McCormick, F.** and Kirn, D. "Adenovirus Mutants with Host Ranges Restricted To Tumor Cells."
1997 **McCormick, F.** "Cancer Therapies Based On Ras And P53 Mutations."
1998 Tetsu, O., Korn, M. and **McCormick, F.** "Regulation of Cyclin D1 and P53 in Colon Cancer Cells" Switzerland.
1999 **McCormick, F.** "Altered Signaling Pathways In Colon Cancer Cells."
1999 **McCormick, F.** "Tumor Therapy with Modified Adenoviruses."
2000 **McCormick, F.** "Cancer Therapy Based On the P53 Pathway."
2000 **McCormick, F.** "Interactions between Ras, Beta-Catenin and P53 Pathways in Human Cancer" Madrid, Spain.
2000 **McCormick, F.**"Interactions Between Ras, beta-catenin and p53 Pathways in Human Cancer." 11th Annual Pezcoller Symposium, Italy.
2000 **McCormick, F.**"Cancer Therapy Based on P53."

2000 **McCormick, F.,** Kirn, D., Heise, K., Sampson-Johannes, A. "ONYX 015: A Potential Oncolytic Virus Specific for p53-Deficient Tumors."AACR Special Conference, Vail, Colorado.
2000 **McCormick, F.** "Adenoviruses with Host Ranges Restricted To Cancer Cells." Berlin, Germany.
2000 **McCormick, F.** "Cancer Therapies based on Ras and p53." Stanford, California.
2000 **McCormick, F.,** O'Shea, C., Shen, J. and Johnson, L. "Virus That Replicate Selectively In Cancer Cells."
2002 **McCormick, F.** "Adenoviruses Selective for Cancer Cells Based on the RB and P53 Pathways."
2002 **McCormick, F.** "Cancer Therapy Based On Ras And Related Proteins." World Congress of Pharmacology, San Francisco, California.
2003 **McCormick, F.** "Cancer Therapy Based on Ras and P53 Pathways." Japan Society of Clinical Oncology, Sapporo, Japan.
2004 **McCormick, F.,** Tetsu, O., Korn, M. and O'Shea, C. "Cancer Therapy Based on Ras and P53 Pathways." Case Western, Cleveland, Ohio.
2004 **McCormick, F.,** Tetsu, O., Korn, M. and O'Shea, C. "The Ras Pathway." University of New Mexico, CMDP Seminar, Albuquerque, New Mexico.
2005 **McCormick, F.**"New Targets in The Ras Pathway."
2005 **McCormick, F.**"The New Era of Targeted Cancer Therapy." Singapore.
2005 **McCormick, F.**"Cancer Therapy Based On the Ras Pathway." Singapore.
2005 **McCormick, F.** "New targets in the Ras pathway."
2006 **McCormick, F.** "Novel Regulators and Effectors of the Ras Pathway."
2006 **McCormick, F.**"Drug Targets in the Ras Pathway." Beatson Conference, Glasgow, Scotland, U.K.
2006 **McCormick, F.** "New Targets." Bay City Capital CEO Conference Cancer Symposium, Phoenix, AZ.
2006 **McCormick, F.** "The Ras Pathway in Cancer." 2006 Annual AACR Meeting, Washington, DC.
2006 **McCormick, F.** "The Success and Failure of Targeted Therapies." Stanford Medical School Cancer Biology Retreat Conference, Asilomar, CA.
2007 **McCormick,F.** "Mutation Detection Strategies for Diagnostics." 2007 AACR Annual Meeting, Los Angeles, CA.
2007 **McCormick, F.** "Drug Targets in the Ras Pathway." 1st International Costello Syndrome Research Symposium, Portland, OR.
2007 **McCormick, F.** "The Success and Failure of Targeted Therapies." 2007 International Melanoma Congress, New York, NY.
2007 **McCormick, F.** "Targeting the Ras Pathway." CNIO (Centro Nacional de Investigacónes Oncologicas) Conference, Madrid, Spain.
2007 **McCormick, F.**"Future Prospects For Targeted Therapies." NCRI (National Cancer Research Institute) Conference, Birmingham, U.K.
2008 **McCormick, F.** "Targeting the Ras Pathway." 19th Annual Cancer Progress Conference, New York, NY.

**RESEARCH PROGRAM:**

**Significant Recent Publications**

1. O'Shea, C., Johnson, L., Bagus, B., Choi, S., Nicholas, C., Shen, A., Boyle, L., Pandey, K., Soria, C., Kunich, J., Shen, Y., Habets, G., Ginzinger, D., **McCormick, F.** 2004. Late viral RNA export, rather than p53 inactivation, determines ONYX-015 tumor selectivity. *Cancer Cell* 6: 611-23.

Nature of Contribution: I supervised Dr. O'Shea, a post-doctoral fellow in my lab, and played a major role in the writing of the paper.

2. Macrae M., Neve R.M., Rodriguez-Viciana P., Haqq C., Yeh J., Chen C., Gray J.W., **McCormick F.** 2005. A conditional feedback loop regulates Ras activity through EphA2. *Cancer Cell* 8: 111-8.

   Nature of Contribution: I supervised Dr. Macrae, a post-doctoral fellow in my lab, and played a major role in the writing of the paper.

3. Rodriguez-Viciana, P., Oses-Prieto, J., Burlingame, A., Fried, M., **McCormick, F**. 2006. A phosphate holoenzyme comprised of shoc2/sur8 and the catalytic subunit of pp1 functions as an M-Ras effector to modulate Raf activity. *Molecular Cell* 22:217-30.

   Nature of Contribution: I supervised Dr. Rodriguez-Viciana, a post-doctoral fellow in my lab, and played a major role in the writing of the paper.

4. Lee, S.H., **McCormick, F**. 2006. p97/DAP5 is a ribosome-associated factor that facilitates Protein synthesis and cell proliferation by modulating the synthesis of cell cycle proteins. *EMBO J* 25: 4008-19.

   Nature of Contribution: I supervised Dr. Lee, a post-doctoral fellow in my lab, and played a major role in the writing of the paper.

5. Kitagawa, M., Lee, S.H., **McCormick, F.** 2008. Skp2 suppresses p53-dependent apoptosis by inhibiting p300. *Mol Cell* 29:217-31.

   Nature of Contribution: I supervised Dr. Lee & M. Kitagawa, a post-doctoral fellow & student in my lab, and played a major role in the writing of the paper.

**RESEARCH PROGRAM SUMMARY**

My research is focused on signal transduction pathways in cancer cells and ways of treating cancer based on these pathways. The Ras pathway has been my primary interest, although we are also interested in metabolic differences between cancer cells and normal cells, as well as defects in cancer proteins related to mitotic checkpoints. My lab is attempting to understand how oncogenic Ras alters cell growth and survival in cancer cells and in cells from patients suffering from neurofibromatosis. The latter disease is caused by loss of a negative regulator of Ras of the Ras GAP family, a family of enzymes that was discovered in my lab. Loss of the neurofibromin protein leads to hyperactivation of Ras in cells of neural crest origin: as a result patients expressing defective neurofibromin suffer from learning defects, multiple benign lesions and an increased risk of certain cancers. We are using a combination of yeast genetics and biochemistry to understand more about the function of neurofibromin and how it is regulated, as well as new ways of treating this terrible disease.

The Ras pathway is negatively regulated by intrinsic pathways that are not well understood, including those involving ephrins and sprout proteins. We are using biochemical methods to elucidate these pathways at the molecular level and hope that this will lead to new ways of blocking Ras activity for therapeutic purposes.

My lab has worked extensively on viruses that kill cancer cells selectively. We are developing this concept using self-amplifying plasmids that replicate in cancer cells specifically, and encode proteins that kill neighboring cancer cells. Plasmid amplification is driven by DNA replication proteins coded by the plasmid itself, and an origin of DNA replication also encoded in the plasmid. The replication protein has been modified to prevent amplification in normal cells, in which RB and p53 block activity.